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Drinking Water Criteria Document for Dichloroethylenes (1,1-Dichloroethylene, cis-1,2-Dichloroethylene, and trans-1,2-Dichloroethylene) (Draft)

(U.S.) Environmental Protection Agency
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DRAFT CRITERIA DOCUMENT

FOR THE

DICHLOROETHYLENES*

(1,1-Dichloroethylene)

(cis-1,2-Dichloroethylene)

(trans-1,2-Dichloroethylene)

DECEMBER, 1984

Criteria and Standards Division

Office of Drinking Water

U.S. Environmental Protection Agency

Washington, D.C.

* This draft criteria document contains information on three dichlorinated ethylenes. At this time, an RMCL for 1,1-dichloroethylene is being proposed. The cis- and trans-1,2-dichloroethylenes are being examined for possible inclusion in Phase II of the revised regulations

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on dichloroethylenes. This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of dichloroethylenes
- Toxicokinetics and human exposure to dichloroethylenes
- Health Effects of dichloroethylenes in humans and animals
- Mechanisms of toxicity of dichloroethylenes
- Quantification of toxicological effects of dichloroethylenes

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PREFACE

This document was prepared for the Criteria and Standards Division, Office of Drinking Water of the U.S. Environmental Protection Agency, Washington, D.C. under Contract 68-02-3659, Work Assignment 02. The EPA Project Officer was Dr. Edward V. Ohanian. The The EPA Lead Reviewer was Dr. Penelope A. Fenner-Crisp.

Dr. John P. Glennon, ICAIR Systems Division, Life Systems, Inc. was the Task Manager for this study. The principal authors of the document, in alphabetical order, were: Dr. P. Frederick Guengerich, Dr. Curtis Klaassen and Dr. Joel Lantz. Dr. David Jenkins was responsible for technical editing and consolidation functions.

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I. SUMMARY

1,1-Dichloroethylene is used industrially as a chemical intermediate and in the manufacture of polyvinylidene chloride copolymers (PVDCs). The impermeability of PVDCs make them useful as barrier coatings in the packaging industry where they are widely used in food wrappings. PVDCs also are used in the manufacture of nonflammable synthetic fibers and are extensively used as interior coatings for tanks, pipes, etc. 1,2-DCEs are not widely used industrially, although they have had limited use as solvents.

The DCEs, like other chlorinated hydrocarbons, cause depression of the central nervous system (CNS). Therefore, exposure to high concentrations of DCEs can cause narcosis and presumably could ultimately cause death due to respiratory depression.

The toxic effects of cis- and trans-1,2-DCE are not well documented. However, 1,1-DCE has been shown to cause liver and kidney injury in animal studies and similar injuries would be expected in prolonged human exposures to high concentrations.

Neither 1,1-DCE nor cis- or trans-1,2-DCE have been shown to be mutagenic without microsomal activation. However, with microsomal activation, 1,1-DCE was found to be mutagenic in bacterial systems, but not in V79 Chinese hamster cells or in dominant lethal studies in mice and rats.

On the basis of the data available to date, IARC (1983) concluded that there is sufficient evidence to state that 1,1-DCE is mutagenic.

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There are no data evaluating the carcinogenic potential of cis- or trans- 1,2-DCE. Preliminary data show that 1,1-DCE produces kidney adenocarcinomas in male Swiss mice and mammary adenocarcinomas in Swiss mice and Sprague-Dawley rats. In addition, 1,1-DCE was shown to be an initiator in the skin papilloma test system in Swiss mice when given with phorbol myristate acetate. However, there was no evidence of carcinogenic potential in several other studies using different strains of mice, rats and hamsters exposed by inhalation or orally.

IARC stated in 1979 that the evidence available at that time indicated that 1,1-DCE caused malignant tumors in mice and rats and that some of the tumors were similar to those caused by vinyl chloride. The evidence is limited, however, by the fact that it is based partly on studies which were still in progress. IARC planned to conduct a reevaluation when the final data from Maltoni, et al. became available along with those from the NTP gavage bioassay and the Dow study. IARC's assessment of the available human data stated that these data were not adequate to permit assessment of 1,1-DCE's carcinogenic potential in the human (IARC, 1983).

EPA recently proposed guidelines for the assessment of carcinogenic risk (U.S. EPA, 1984b). Applying these proposed guidelines, the Office of Drinkng Water determined, in a preliminary assessment, that the available data on the carcinogenic and mutagenic potentials of 1,1-dichloroethylene directs its characterization of its carcinogenic potential into Group C: Possibly Carcinogenic to Humans.

II. GENERAL INFORMATION AND PROPERTIES

A. Physical and Chemical Properties

Dichloroethylenes consist of three isomers: 1,1-dichloroethylene, cis-1,2-dichloroethylene and trans-1,2-dichloroethylene. All isomers of dichloroethylene are clear, colorless liquids with the molecular formula $C_2H_2Cl_2$ and a molecular weight of 96.95 (Windholz et al., 1976; Hardie, 1964).

1,1-Dichloroethylene. The isomer 1,1-dichloroethylene (also referred to as vinylidene chloride, 1,1-dichloroethene, DCE and VDC) dissolves in organic solvents and is soluble in water to 400 mg/l at 20°C (Irish, 1963). Other estimates of 1,1-DCE's solubility in water range from 0.01 wt% (10 mg/l) to 0.64 wt% (640 mg/l) at temperatures varying from 4-25°C (Weiner, 1951; Hardie, 1964; Ley et al., 1967; Wessling and Edwards, 1971; Jaeger and Stringer, 1972). More recently, DeLassus and Schmidt (1981) determined that the solubility of 1,1-DCE was nearly constant at 0.25 wt% (250 mg/l) over the range of 15-90°C. For air concentrations, one (1) ppm is equivalent to 3.97 mg/m^3, and one (1) mg/l is equivalent to 252 ppm, when measured at 25°C and 760 mm Hg (Irish, 1963). It is extremely volatile, having a vapor pressure of 591 Torr (mm Hg) at 20°C and a boiling point of 31.5°C. It has a melting point of -122.1°C and a mild, sweet odor similar to that of chloroform. The liquid is heavier than air and will, therefore, settle in low places in a still atmosphere. It is also flammable, with 7.3-16.0% explosive limits in air at 28°C. The monomer polymerizes to a plastic at temperatures above

0°C, especially in the presence of oxygen or other catalysts. It also forms explosive peroxides in contact with air. Therefore, it is stored and shipped either with an inhibitor (e.g., 200 ppm of monomethyl ether of hydroquinone) or is refrigerated under an inert gas in the absence of light and air (Warren and Ricci, 1978; Windholz et al., 1976; Hardie, 1964). The octanol/water partition coefficient for 1,1-dichloroethylene was reported as 5.37 (log P = 0.73) by Radding et al. (1977), indicating that it should not accumulate significantly in aquatic animals (U.S. EPA, 1980).

None of three listings of azeotropes (the first of which is extensive) indicates that 1,1-dichloroethylene forms azeotropes with water (Horsely, 1947; Lange and Forker, 1961; Perry and Chilton, 1973), although it does form an azeotrope with methanol. Azeotropes occur infrequently between compounds with boiling points differing by more than about 30°C (Perry and Chilton, 1973). Therefore, formation of an azeotrope between 1,1-dichloroethylene (31.5°C boiling point) and water (100°C boiling point) is unlikely to occur, eliminating this as a concern during possible evaporative purification of water from the chemical.

1,2-Dichloroethylene. This isomer is sometimes referred to as acetylene dichloride, 1,2-dichloroethene, sym-dichloroethylene and dioform. The marketed product is generally a mixture of cis- and trans- isomers. Both the cis- and trans- isomers are soluble in water (solubilities of 3,500 mg/l and 6,300 mg/l at 25°C, respectively), but readily soluble in most organic solvents. 1,2-Dichloroethylene is volatile, though less so than 1,1-dichloroethylene. The cis- isomer has a vapor pressure of 180 Torr (mm Hg) at 20°C and boils at 60°C. The trans- isomer has a vapor pressure of 265 Torr (mm Hg) at 20°C and a boiling point of 47°C. The vapor densities are identical to that of 1,1-dichloroethylene, which is over three times that of air (Windholz et al., 1976; Irish, 1963; Hardie, 1964; Lange and Forker, 1961). 1,2-Dichloroethylene is gradually decomposed by air, light and moisture, forming hydrogen chloride (HCl). The trans- form is noticeably subject to air oxidation (Windholz et al., 1976).

1,2-Dichloroethylenes form azeotropes with water. This factor must be evaluated if evaporative purification of water from these isomers is considered. Horsely (1947) lists a binary azeotrope for cis-1,2-dichloroethylene with water (3.35% water by weight, boiling at 55.3°C) and a ternary azeotrope of this substance with water and ethanol (2.85% water, 90.5% cis-1,2-dichloroethylene and 6.65% ethanol by weight, boiling at 53.8°C). Azeotropes with ethanol and methanol alone also are formed.

Horsely (1947) similarly lists a binary azeotrope for trans-1,2-dichloroethylene with water (1.9% water by weight, boiling at 45.3°C) and a ternary azeotrope with water and ethanol (1.1% water, 94.5% trans-1,2-dichloroethylene and 4.4% ethanol by weight). The trans- isomer, like the cis- isomer, also forms an azeotrope with ethanol alone.

B. Manufacturing and Uses

1,1-Dichloroethylene. Mid-1970's annual production of 1,1-dichloroethylene approximated 120,000 metric tons (Arthur D. Little, Inc., 1976). It is used primarily in the production of polyvinylidene chloride polymers and copolymers (PVDC's), but also as a chemical intermediate in the synthesis of methylchloroform. Other monomers used with 1,1-dichloroethylene in copolymer production are vinyl chloride, acrylonitrile, and alkyl acrylates. The impermeability of PVDC's make them useful primarily as barrier coatings on paper products and plastic films. Polymers containing 1,1-dichloroethylene are widely used in the food packaging industry. [FDA regulations require that for polyvinylidene chloride (PVDC) copolymer coatings on polyolefin, nylon and polycarbonate films contacting food, chloroform soluble extractives may not exceed 0.5 mg/in^2, as extracted under conditions specific to the application (CFR, 1981). No such regulations were found for pure PVDC]. They are likewise used as binders for nonwoven fabrics, paint and concrete. 1,1-Dichloroethylene polymers have been used extensively as interior coatings for ship tanks, railroad cars, and fuel storage tanks and for coating of steel pipes and structures (Wessling and Edwards, 1970; Hardie, 1964). The literature provides no quantitative information as to the concentration of the monomer, although this would be expected to be quite low following processing of the basic resin (e.g., coating, film, formation, storage).

1,2-Dichloroethylene. 1,2-Dichloroethylene is used as a solvent for such substances as rubber, fats, phenol and camphor and for retarding fermentation. It is also used as a low temperature extraction solvent for heat sensitive substances and has been employed as a coolant in refrigeration plants (Windholz et al., 1976; Hardie, 1964). No production figures have been found, although in the previous decade Irish (1963) indicated that neither isomer had developed wide industrial usage.

C. Extent and Significance of Problem

1,1-Dichloroethylene. Annual emissions of 1,1-dichloroethylene were estimated in 1975 to be 1.3 million lb/year, primarily from monomer production process vents and spills and from polymer production and processing. This chemical is expected to be short-lived in water because of its poor solubility and rapid volatilization to the atmosphere (Hushon and Kornreich, 1976). Its tendency to form peroxides spontaneously in the presence of air or oxygen (Barr and Watts, 1972; Wessling and Edwards, 1970) would be expected to limit its persistence in the atmosphere.

However, Pearson and McConnell (1975) indicate that degradation of such compounds dissolved in water is much slower than in the atmosphere. They estimate a tropospheric half-life of eight weeks. 1,1-Dichloroethylene in air decomposed to carbon monoxide (CO), carbon dioxide (CO_2) and hydrogen chloride (HCl) when irradiated at wavelengths of light simulating atmosphere exposure (Pearson and McConnell, 1975). Therefore, those compounds may be the primary degradation products of 1,1-dichloroethylene in the natural atmosphere as well. The results of a sampling/analysis-method study of the air around or near industrial/waste disposal areas of the U.S. has been reported (Pellizzari, 1978). In general, the concentrations of 1,1-dichloroethylene in the air were low (typically <1 ug/m^3). Concentrations in drinking water, detected in water supplies of four out of ten cities in the U.S., were also low (e.g., 0.1 ug/l) as shown in Table II-1 (U.S. EPA, 1975).

1,2-Dichloroethylene. In view of their slow decomposition by air, light and moisture (Windholz *et al*., 1976), the 1,2-dichloroethylenes would be expected to be removed slowly from the environment. The tropospheric half-lives of the isomers are likely to be the same order of magnitude as estimated by Pearson and McConnell (1975) for 1,1-dichloroethylene (eight weeks). 1,2-Dichloroethylene has been detected in a limited number of U.S. drinking water supplies, as shown in Table II-1 (U.S. EPA, 1975).

Table II-1

Summary of Dichloroethylene Concentrations in Finished Drinking Waters at Ten Areas of the United States[a]

Area	Concentration, ug/l 1,1-Dichloroethylene	 cis 1,2-Dichloroethylene	 trans 1,2-Dichloroethylene
Miami, FL	D[b], 0.1	D[b], 16.0	D[b] 1.0
Seattle, WA	ND[c]	ND	ND
Ottumwa, IA	ND	ND	ND
Philadelphia, PA	D[b], 0.1	D[b], 0.1	ND
Cincinnati, OH	D[b]	D[b], 0.1	ND
Tucson, AR	ND	ND	ND
New York, NY	ND	ND	ND
Lawrence, MA	D[b]	ND	ND
Grand Forks, ND	ND	ND	ND
Terrebonne, Parish, LA	ND	ND	ND

[a] From U.S. EPA, 1975, Table I-3

[b] Detected by 500 ml volatile organic analysis but not quantified

[c] Not detected

III. KINETICS

A. Absorption

Dichloroethylenes are neutral, low molecular weight, lipid soluble materials which should be absorbed readily following any route of administration.

Kinetic studies based on urinary and biliary excretion data have shown that administration of a single oral dose of 1,1-dichloroethylene in the dose range 0.5-50 mg/kg results in rapid and complete absorption (Jones and Hathway, 1978a; McKenna et al., 1978b; Reichert et al., 1979). Rapid absorption and distribution of 1,1-DCE after intravenous or intraperitoneal administration also have been demonstrated (Jones and Hathway, 1978a).

It is well established that the absorption of gases from the lung is highly dependent on the blood:gas partition coefficient. As shown in Table III-1 all three dichloroethylenes probably have a blood:gas partition coefficient in the range of 5-10, indicating that the materials equilibrate like a soluble vapor. These chemicals in inspired air have been shown to come to a steady-state with the whole animal within 1-2 hours (Table III-1). The rate constant for reaching equilibrium has been determined to be 2.2 hr^{-1} (Andersen et al., 1979b). The blood:gas solubility of these compounds combined with the observation that they have a relatively short equilibration time suggests that they do not concentrate in poorly perfused tissues. Using relatively new kinetic procedures, a mixed partition coefficient (S), which is defined as the concentration of the chemical in the richly perfused tissues divided by its concentration in the gas phase, has been determined for these

Table III-1

Correlation of Physical and Chemical Characteristics to Inhalation Absorption and Distribution of Dichloroethylenes

	Blood:gas Partition Coefficient	Whole Body Equilibration Time, hr	Mixed Partition Coefficients	Equilibration Constant K_{eq}	Boiling Point, °C
cis-1,2-DCE	9.2[a]	2[b]	-	20[b]	60
trans-1,2-DCE	5.8[a]	1.5[b]	10.9[c]	11.5[b]	47
1,1-DCE	-	1[b,c]	4.0[c]	7.8[b]	31.5

[a] Sato and Nakajima, 1979. Data determined in experiments using human blood.
[b] Pilser and Bolt, 1979. Data determined in experiments using rats.
[c] Andersen _et_ _al_., 1980a. Data determined in experiments using rats.

chemicals (Andersen et al., 1980a), As can be seen from Table III-1 rats exposed to trans-1,2-DCE have been shown by this method to absorb more chemical at equilibrium than rats exposed to 1,1-DCE. A similar kinetic analysis of the distribution of these chemicals has been performed (Filser and Bolt, 1979). They determined the equilibration constant (K_{eq}), which is defined as the clearance of a chemical from the chamber into the animal relative to clearance from the animal into the chamber, for all three chemicals. The data for K_{eq} in Table III-1 show that, at equilibrium, the amount of chemical present in animals exposed to the dichloroethylenes would be cis-1,2-DCE > trans-1,2-DCE > 1,1-DCE. This study found an empirical relationship between K_{eq} and the volatility of the toxicant for a wide variety of halogenated ethylenes. Using the boiling point as a measure of volatility, it was shown that compounds with low boiling points have lower concentrations in tissue than those of higher boiling points. Thus, 1,1-DCF which has the lowest boiling point, would be expected to show the lowest concentration in tissue and cis-1,2-DCE, which has the highest boiling point, would be expected to have the highest concentration in tissues (Table III-1).

Dallas, et al. (1983) measured 1,1-dichloroethylene concentrations in blood samples from the femoral veins of anesthetized male Sprague-Dawley rats inhaling 25, 75, 150 or 300 ppm of 1,1-dichloroethylene. Absorption was very rapid and substantially increased blood concentrations (about 25% of steady state) were present by 2 minutes. Equilibrium levels were reached by approximately 30 minutes for the three lower doses, while blood levels tended to increase gradually over three hours for animals exposed to the highest concentration (300 ppm).

B. Tissue Distribution

The distribution of 1,1-DCE to various organs of rats following inhalation exposure for 2 hours at an initial concentration of 2000 ppm has been studied using [^{14}C]1,1-DCE (Jaeger *et al.*, 1977a). Many studies with 1,1-DCE have been performed using both fed and fasted animals because 1,1-DCE is known to be more hepatotoxic in fasted animals (Jaeger *et al.*, 1974). The concentration of total radioactivity 30 minutes after cessation of exposure was highest in the blood followed by kidney, liver, spleen, heart and brain in both the fed and fasted rats. The distribution of trichloroacetic acid insoluble labeled material, hereafter referred to as covalently bound material, followed a similar pattern with the following exceptions. Whereas the kidney contained very little covalently-bound ^{14}C, approximately one-third of the ^{14}C in the liver was covalently bound (Jaeger, *et al.*, 1977a).

Similar studies have been conducted on rats 72 hours after inhalation exposure to either 10 or 200 ppm [^{14}C]1,1-DCE for 6 hours (McKenna, *et al.*, 1977, 1978a). The data on the distribution of ^{14}C in different tissues are in Table III-2. At either exposure level, the highest concentration of ^{14}C was found in the liver and kidney. When tissue concentration data were normalized to account for differences in end-exposure body burdens, the greatest percentage of the body burden per gram of tissue was found in the kidney, liver and lung and was consistently higher in fasted rats at both exposure levels. Only a small amount of the ^{14}C

Table III-2

Relative Amounts of ^{14}C in Tissues 72 Hr After Exposure to 10 or 200 ppm [^{14}C]1,1-DCE for 6 Hr.

Microgram Equivalents of [^{14}C]1,1-DCE per gram of Tissue

	10 ppm		200 ppm	
Tissue	**Fed Rats**	**Fasted Rats**	**Fed Rats**	**Fasted Rats**
Liver	0.56 (0.075)	0.57 (0.097)[a]	15.75 (0.147)	19.57 (0.204)[a]
Kidney	1.68 (0.228)	1.85 (0.314)[a]	3.15 (0.079)	19.90 (0.208)[a]
Lung	0.19 (0.026)	0.21 (0.036)[a]	5.19 (0.044)	7.12 (0.074)[a]
Fat	0.07	0.06	0.74	1.25
Muscle	0.06	0.04	0.91	1.19
Skin	0.19	0.15	3.78	5.98
Carcass	0.08	0.06	1.68	2.18
Plasma	0.15	0.16	3.15	5.20[a]

( ) Represent tissue burdens normalized for differences in end-exposure body burden of ^{14}C activity. Microgram equivalents of [^{14}C]1,1-DCE per gram of tissue/total milligram equivalents recovered per rat.

[a] Significantly different from fed rats of the same exposure group, $p<0.05$, Student's t test.

Based on McKenna et al., 1978a.

was found in the fat. Table IV-3 compares the extent of covalent binding of ^{14}C and the total biotransformation of 1,1-DCE. A comparison of fed and fasted rats at the different exposure concentrations shows that the concentration of covalently bound ^{14}C in the liver increases in 1,1-DCE biotransformation. Although fasted rats metabolize less 1,1-DCE than fed rats, the concentration of covalently bound ^{14}C activity in the liver was greater in fasted than fed rats following exposure to 200 ppm. The increase in covalent binding in the livers of fasted rats was more apparent after normalization of the data to account for differences in the biotransformation of 1,1-DCE (B/A ratio, Table IV-3).

Distribution of 1,1-DCE to the organs of rats following intragastric administration of 25 mg/kg bw of [^{14}C]1,1-DCE also has been studied (Jones and Hathway, 1978a). Sequential autoradiograms of longitudinal sagittal sections through whole animals showed large ^{14}C concentrations in the kidneys and liver after 30 minutes and a more general distribution of ^{14}C throughout the soft organs of the body at 1 hour. The kidneys and liver retained ^{14}C for the longest time after dosing.

Distribution studies also have been conducted with rats 72 hours after administration of a single oral dose of 1 or 50 mg/kg [^{14}C]1,1-DCE (McKenna et al., 1978b). The distribution of ^{14}C to different tissues (Table III-4) was shown to be independent of dose and not to be influenced by fasting the animals. The greatest percentage of the ^{14}C dosage per gram of tissue 72 hours after administration was found in the liver. Table III-5 compares the extent of covalent binding of ^{14}C to hepatic tissue macromolecules with the

Table III-3

Metabolism of $[^{14}C]$1,1-DCE and Covalent Binding of ^{14}C to Rat Hepatic Tissue After Inhalation Exposure to 10 or 200 ppm of $[^{14}C]$1,1-DCE.

Concentration and Pretreatment	Body Burden (mg of $[^{14}C]$1,1-DCE/kg)	(A) Metabolized $[^{14}C]$1,1-DCE (mgEq/kg)	(B) Microgram Equivalents of $[^{14}C]$1,1-DCE bound per gram of liver protein	B/A
10 ppm				
Fed	2.89	2.84	2.49	0.88
Fasted	2.30	2.26	2.47	1.10
200 ppm				
Fed	44.53	42.73	64.18	1.49
Fasted	35.93[a]	32.92[a]	79.46	2.47[a]

[a] Significantly different than fed rats exposed to the same concentration of 1,1-DCE, $p<0.05$, Students test.

Based on McKenna et al., 1978a.

Table III-4

Relative Amounts of ^{14}C in Tissues After a Single Oral Dose of 1 or 50 mg/kg of $[^{14}C]$1,1-DCE[a]

Tissue	1 mg/kg Fed	1 mg/kg Fasted	50 mg/kg Fed	50 mg/kg Fasted
Liver	0.063	0.101	0.089	0.073
Kidney	0.030	0.028	0.018	0.033
Lung	0.013	0.001	0.003	0.019
Fat	0.014	0.108	ND	ND
Muscle	0.007	0.005	ND	ND
Skin	0.018	0.014	0.009	0.015
Carcass	0.008	0.008	0.006	0.007
Whole Blood	0.013	0.011	0.013	0.016

[a] Expressed as percentage of dose per gram of tissue

ND = Not detectable above background

Based on McKenna et al., 1978b

Table III-5

Metabolism of $[^{14}C]$1,1-DCE and Covalent Binding of ^{14}C to Rat Hepatic Tissue After a Single Oral Dose of $[^{14}C]$1,1-DCE

Dose and Pretreatment	(A) Metabolized $[^{14}C]$1,1-DCE (mgEq/kg)	(B) Covalently bound 1,1-DCE (ug Eq of $[^{14}C]$1,1-DCE/ gram liver protein	B/A
1 mg/kg			
Fed	0.956	0.854	0.89
Fasted	0.924	0.861	0.93
50 mg/kg			
Fed	39.08	37.67	0.96
Fasted	31.86	44.45	1.40[a]

[a] Significant fed vs fasted difference, p <0.05, Student's test.

Based in McKenna *et al.*, 1978b

amount of [^{14}C]1,1-DCE biotransformed. No statistically significant differences for covalent binding on a per gram protein basis were observed between fed and fasted animals at either dose level. Normalization of the data to account for differences in biotransformatio (B/A, Table III-5) showed an increase in the amount of ^{14}C covalently bound to liver macromolecules in fasted rats at the 50 mg/kg level.

Subcellular distribution of [^{14}C] 30 minutes following inhalation of 2,000 ppm of [^{14}C]1,1-DCE for 2 hours was determined in the microsomal, mitochondrial and cytosolic compartments of the liver (Jaeger et al., 1977a). More ^{14}C was found in liver fractions from fasted rats than from fed rats. There was no marked subcellular localization of ^{14}C, since its concentration was about the same in mitochondria, cytoplasm and microsomes. The ^{14}C found in microsomes and mitochondria was largely covalently bound (TCA-insoluble). In contrast, the cytosol contained substantial amounts of TCA-soluble ^{14}C, suggesting the presence of metabolites. Significant amounts of the ^{14}C in microsomes and mitochondria was $CHCl_3$-soluble, suggesting that there is considerable binding of ^{14}C to lipids. The turnover rate of TCA-insoluble radioactivity derived from 1,1-DCE has a half-life of 2-3 hours.

Distribution data on 1,2-DCE isomers are not available.

C. Biotransformation

The comparative biotransformation of chloroethylenes has been studied extensively. Metabolic end products of chlorinated ethylenes are predominantly alcohols and carboxylic acids. Perfusion of either cis-1,2-DCE or trans-1,2-DCE in isolated rat liver produced detectable amounts of dichloroethanol and dichloroacetic acid (Bonse _et_ _al_., 1975), possibly indicating the initial formation of dichloroacetaldehyde. The biotransformation of the cis-isomer relative to the quantity taken up by the liver was much greater than the trans-isomer. Chloroacetic acid has been identified as a product in the biotransformation of 1,1-DCE in perfused rat liver. Inhibition of epoxide hydrase in _in_ _vitro_ studies using rat liver S-9 resulted in a stimulation of chloroacetic acid formation from 1,1-DCE, leading to the conclusion that the glycol intermediate is relatively unimportant in the conversion of 1,1-DCE to chloroacetic acid (Leibman and Ortiz, 1977). Additionally, studies using competitive epoxide substrates have shown that epoxide hydrating pathways are of minimal significance in the biotransformation of reactive intermediates of 1,1-DCE (Andersen _et_ _al_., 1980b).

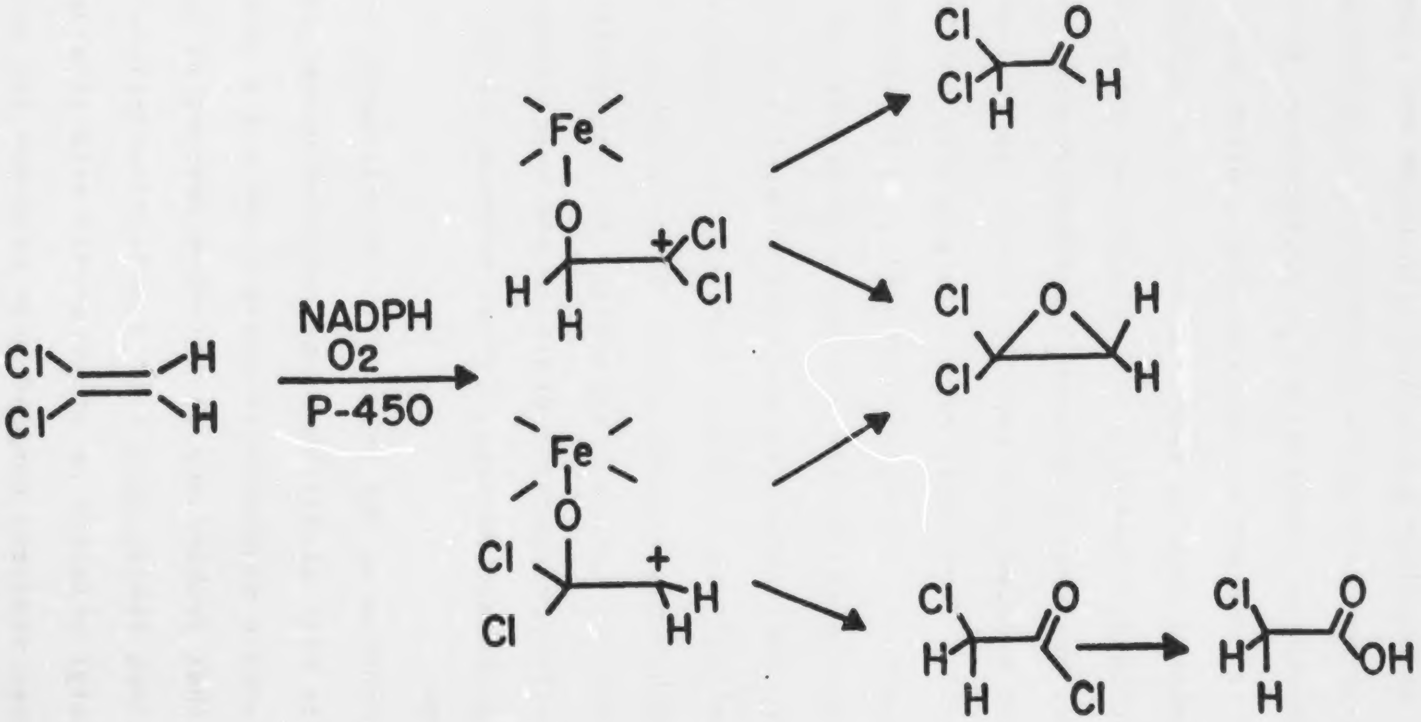
Although much speculation concerning the role of the epoxide of 1,1-dichloroethylene (2,2-dichloroethylene oxide) had been made in the earlier literature, the compound had not been synthesized and examined. Liebler and Guengerich (1983) synthesized this epoxide and characterized it using NMR (^{13}C,^{1}H) and mass spectral techniques. The compound is highly unstable in water and decomposes to form a variety of products;2-chloroacetic acid and glycolic acid are formed at very low pH;carbon monoxide, formaldehyde and formic acid are formed at neutral and basic pH. These compounds are inconsistent with the known metabolites of the microsomal oxidation of 1,1-dichloroethylene, which are chloroacetic acid and dichloroacetaldehyde (Liebler and Guengerich, 1983).

Dichloroacetaldehyde was not formed under these conditions or when the 2,2-dichloroethylene oxide was added in stoichiometric amounts to purified cytochrome P-450. While it was possible to form dichloroacetaldehyde from 2,2-dichloroethylene oxide in organic solvents in the presence of very high concentrations of ferric bromide, complexation of the iron into a model porphyrin to model the enzyme abolished its ability to cause this rearrangement. The ratio of the products 2,2-dichloroacetaldehyde and chloroacetic acid (and suicide inactivation of cytochrome P-450) varied among a number of different cytochrome P-450 enzymes, in lack of accordance with the view that an epoxide intermediate forms all of these metabolites. Low levels of the epoxide were trapped in microsomal reactions with a nucleophile;however, the levels of epoxide formed were at least an order of magnitude too low to support the obligate intermediary of an epoxide in the formation of the other products of 1,1-dichloroethylene biotransformation.

A scheme for the biotransformation of 1,1-dichloroethylene based on the work of Liebler and Guengerich (1983) is shown in Figure III-1. The formal chloride shift has precedent in previous work with 1,1,2-trichloroethylene (Miller and Guengerich, 1982), where evidence against the role of an epoxide in the formation of chloral (2,2,2-trichloroacetaldehyde) also was found. However, formation of 2,2-dichloroacetaldehyde requires a formal hydride shift. Deuterium studies showed that such a shift did occur (Liebler and Guengerich, 1983). The occurrence of such hydride shifts without epoxides in other non-halogen systems involving cytochrome P-450 and other oxidations now has been demonstrated (Grove and Myers, 1983;Liebler and Guengerich, 1983;Mansuy, et al., 1984).

Figure III-1

Metabolic Pathways Involved in Oxidation of 1,1-Dichloroethylene by Cytochrome P-450


NADPH
O2
P-450
Fe
Cl
H
O
OH
+

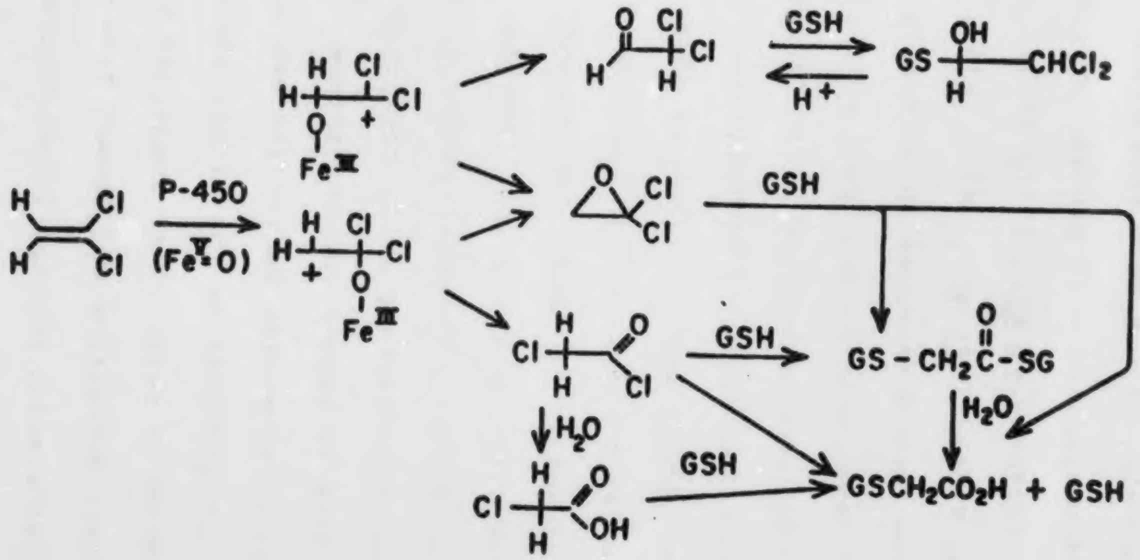
Adapted from Liebler and Guengerich, 1983.

Other recent studies have shed some light on the nature of the primary glutathione conjugates which are formed. Rat liver microsomal incubations fortified with NADPH and glutathione formed three glutathione conjugates subsequently isolated and identified as S-(2,2-dichloro-1-hydroxy)ethyl glutathione, S-(2-glutathionyl) acetyl glutathione and S-carboxymethyl glutathione (Figure IV-2). The first adduct results from the reaction of 2,2-dichloroacetaldehyde with glutathione. However, this adduct was not found in isolated hepatocytes, presumably because 2,2-dichloroacetaldehyde is oxidized and reduced more rapidly than it is conjugated (Liebler, *et al.*, 1984). Thus, this adduct is probably not formed *in vivo*. The second adduct, s-(2-glutathionyl) acetyl glutathione, is only partially stable (half-life = 4 hours at neutral pH in buffer) and probably corresponds to the unknown acetyl derivative postulated by Jones and Hathway (1978a). The compound hydrolyzes to form S-carboxymethyl glutathione which can be processed further in the body to yield the urinary metabolites thiodiglycolic acid, N-acetyl-S-(2-hydroxyethyl) cysteine and N-acetyl-S-(2-carboxymethyl) cysteine (Jones and Hathway, 1978a; McKenna, et al., 1978a; Reichert, *et al.*, 1979).

The identity of the primary 1,1-dichloroethylene metabolite which reacts with glutathione has not been unambiguously proven; however, kinetic studies with glutathione and a model thiol indicated that 2-chloroacetyl chloride reacted at least one thousand times faster than diol 2,2-dichlorethylene oxide, 2-chloroacetyl chloride or chloroacetic acid (Liebler, *et al.*, 1984). These studies, coupled with evidence for only low level transformation of the epoxide to 2-chloroacetyl chloride at pH

Figure III-2

Oxidation of 1,1-Dichloroethylene and Conjugation with Glutathione (GSH)


P-450
(Fe^{V}=O)
Fe^{III}
GSH
H+
GS–CH₂C(=O)–SG
H₂O
GSCH₂CO₂H + GSH

Adapted from Liebler _et_ _al_., 1984.

greater than 2 (Liebler and Guengerich, 1983), would suggest that the most prominent aspect of the biotransformation of 1,1-dichloroethylene is the transfer of chloride ion in the cytochrome P-450 intermediate to form 2-chloroacetyl chloride and the subsequent reaction of that species with glutathione or protein.

In live animals, it has been established that 1,1-DCE metabolites are conjugated with glutathione, presumably a detoxication process (McKenna et al., 1977, 1978a, 1978b; Jones and Hathway, 1978a; Reichert et al., 1978, 1979). The major urinary metabolites have been determined in several studies. McKenna, et al. (1978a, 1978b) have isolated four main metabolites in rat urine, two of which they have identified: thiodiglycolic acid and the mercapturic acid N-acetyl-S-(2-hydroxyethyl) cysteine which was present in the highest amount. Both of these materials presumably would be formed as a result of conjugation of one of the metabolites with glutathione. Jones and Hathway (1978a) have found two major metabolites in rat urine: besides thiodiglycolic acid they postulated N-acetyl-S-cysteinyl-acetyl derivative. In addition, they have shown chloroacetic acid, dithioglycolic acid and thioglycolic acid in lesser concentrations. The formation of the N-acetyl-S-cysteinyl-acetyl derivative was unexpected, since this material was not produced in the biotransformation of chloroacetic acid administered in rats. This suggested that the N-acetyl-S-cysteinyl-acetyl derivative was formed from an earlier metabolite than chloroacetic acid, perhaps 1,1-dichloroethylene oxide or chloroacetyl chloride, which was conjugated with glutathione. Reichert et al. (1979) identified three metabolites in rat urine:

thioglycolic acid, the major metabolite, N-acetyl-S-(2-carboxymethyl) cysteine and methylacetylaminoethanol. In addition, three unidentified materials were present in lesser concentrations. The identification of methylthioacetylaminoethanol suggests that, in addition to glutathione conjugation, a totally different reaction mechanism must exist which leads to the formation of ethanolamine derivatives. The ethanolamine is postulated to originate from membrane lipids which react with 1,1-DCE epoxide or other metabolites.

In the intact animal, several studies have shown that a large portion of systemically absorbed 1,1-DCE is metabolically converted in rats. Table III-6 summarizes the data on disposition and biotransformation. The fifth column indicates the percent of the dose excreted into the air as CO_2 and is a reflection of the amount biotransformed. Thus, as the dosage is increased a larger absolute amount of metabolite is formed, but a lesser percentage of the administered dose is biotransformed. This was observed after various routes of administration such as oral, intraperitoneal and inhalation. These data show that the biotransformation of 1,1-DCE is readily saturable. As the dose is increased and biotransformation reaches saturation, more parent compound is excreted into the air (Table III-6). Additionally, fasting the animals for several hours prior to dosing also influenced the biotransformation. Fasted rats had lower body burdens at the end of the experiments and biotransformed less of their body burden than normally fed rats.

Studies comparing the relative ability of mice and rats to biotransform 1,1-DCE have been conducted. Disposition of ^{14}C from [^{14}C]1,1-DCE in mice and rats is shown in Table IV-7 (McKenna,

Table III-6

Disposition and Metabolism of $[^{14}C]$1,1-Dichloroethylene in Rats

		Time	% of Original Dose of $[^{14}C]$ Activity					
Dose mg/kg	Route	After Dose	Pulmonary 1,1-DCE	Excretion CO_2	Renal Excretion	Biliary Excretion	Residual in Body	Refere
0.5	oral	72	1.26	13.64	43.55	15.74	5.57	Reicher
5	oral	72	9.70	11.35	53.88	14.54	2.83	et al.
50	oral	72	16.47	6.13	42.11	7.65	2.77	1979
0.5	oral	72	0.9	23	52		2-4	Reicher
50	oral	72	20	6	36			& Werne
								1978
0.5	oral	0-24	0.6	3.9	71.3	5.1		Jones a
		24-48	0.06	0.5	5.3	2.7		Hathway
		48-72	0.08	0.5	3.6	0.6		1978a
		Total	0.07	4.8	80.2	8.3		
0.5	iv	0-24	80.0	3.5	14.4	0.3		Jones a
		24-48	0	0	0.7	0.1		Hathway
		48-72	0	0	0	0		1978a
		Total	80.0	3.5	15.0	0.4		
0.5	ip	0-24	11.4	2.6	65.8	14.2		Jones a
		24-48	0.2	0.5	2.0	1.6		Hathway
		48-72	0.1	0.5	1.2	0.4		1978a
		Total	11.7	3.6	69.0	16.2		
350	oral	0-24	62.4	0.3	17.6	0.4		Jones a
		24-48	4.8	0.4	10.0	0.5		Hathway
		48-72	0.1	0.3	1.9	0.4		1978a
		Total	67.3	1.0	29.5	1.3		
350	ip	0-24	90.5	0.7	7.1	0.5		Jones a
		24-48	0.6	0.5	0.3	0.1		Hathway
		48-72	0	0.1	0.3	0.1		1978a
		Total	91.1	1.3	7.7	0.7		
1	oral[a]	72	2.89	10.85	62.68	16.25	3.18	McKenna et al. 1978b
1	oral[b]	72	1.36	7.82	66.42	11.18	3.46	
50	oral[a]	72	18.75	4.16	46.62	4.14	2.39	

Table III-6(Continued)

			% of Original Dose of [^{14}C] Activity					
Dose mg/kg	Route	Time After Dose	Pulmonary 1,1-DCE	Excretion CO_2	Renal Excretion	Biliary Excretion	Residual in Body	Referenc
50	oral[b]	72	29.23	3.19	34.88	4.28	3.08	
2.89[c]	inhal[a]	72	1.63	8.74	74.72	9.73	4.75	McKenna *et al.*, 1977, 1978a
2.30[d]	inhal[b]	72	1.60	8.27	78.19	6.75	5.28	
44.53[c]	inhal[a]	72	4.17	8.22	74.66	6.39	6.18	
35.39[d]	inhal[b]	72	8.36	7.24	70.41	2.72	10.52	
e	inhal[a]	24			36.7			Jaeger *et al.*, 1977a
e	inhal[b]	24			36.5			

---

[a] Fed rats

[b] Fasted rats

[c] Total body burden after 6 hr exposure to 10 ppm

[d] Total body burden after 6 hr exposure to 200 ppm

[e] Exposure for 2 hours to gas with initial concentration of 2000 ppm

Table III-7

Disposition of $[^{14}C]$ Following Inhalation of 10 ppm 1,1-DCE Over a 48 Hour Period

	Mice	Rats
Expired 1,1-DCE %	0.65 ± 0.07	1.63 ± 0.14
Expired $^{14}CO_2$ %	4.64 ± 0.17	8.74 ± 3.72
Body Burden %		
Urine	80.83 ± 1.68	74.72 ± 2.30
Feces	6.58 ± 0.81	9.73 ± 0.10
Carcass	5.46 ± 0.41	4.75 ± 0.78
Cage Wash	1.83 ± 0.84	0.44 ± 0.28
Body Burden mg. eq. 1,1-DCE/kg	5.30 ± 0.75	2.89 ± 0.24
Total Metabolized mg. eq. 1,1-DCE/kg	5.27 ± 0.74	2.84 ± 0.26

Based on McKenna *et al.*, 1977b.

These data show that the mouse develops a higher body burden of 1,1-DCE or metabolites than the rat at identical exposure levels (10 ppm). The disposition of 1,1-DCE appears quite similar in the two species. However, as a result of the overall greater rate of biotransformation,covalently bound 1,1-DCE metabolites are higher in the mouse than in the rat as shown in Table III-8 . The substantial difference in biotransformation may be responsible for the different sensitivity of the two species to the carcinogenic effects of 1,1-DCE (Hathway, 1977) since mice, which metabolize more 1, 1-DCE than rats, are more sensitive than rats.

In a study where mice and rats were administered an oral dose (50 mg/kg) of 1,1-DCE, mice were found to metabolize a greater proportion (Jones and Hathway, 1978b). Although 1,1-DCE was biotransformed in much the same way in both species (Table III-9), mice formed considerably more of the N-acetyl-S-cysteinyl-acetyl derivative, and excreted a small amount of N-acetyl-S-(2-carboxymethyl)-cysteine, which was not found in rats. It was suggested that the efficiency of DCE biotransformation follows the activity of the cytochrome P-450 systems in the livers of these animals and that "real exposure," expressed in the amount biotransformed, is higher for orally dosed mice than rats.

Studies of the effects of various inducers and inhibitors of microsomal enzymes on the rate of biotransformation of 1,1-DCE have been conducted using isolated perfused livers (Reichert and Henschler, 1978; Reichert _et_ _al_., 1978) and whole animals (Andersen _et_ _al_., 1979b). The results of these studies are summarized in Table III-10. These studies show contradictory results for the effects of pheno-

Table III-8

Covalently Bound ^{14}C in Rat and Mouse Following Exposure to 10 ppm [^{14}C]-1,1-DCE

	^{14}C-1,1-DCE, ug eq/mg Protein	
	Liver	Kidney
Mice	22.29 ± 3.77	79.55 ± 19.11
Rats	5.28 ± 0.14	13.14 ± 1.15

Based on McKenna *et al.*, 1977b

Table III-9

Relative Proportion of $[^{14}C]$ Excretory Products After Oral Administration of 50 mg/kg of $[^{14}C]$1,1-DCE to Rodents

$[^{14}C]$ Excretory Products	^{14}C Expressed as % of Dose Mice	 Rats
Unchanged DCE pulmonary	6	28
CO_2 excretion	3	3.5
Chloroacetic acid	0	1
Thiodiglycolic acid	3	22
Thioglycolic acid	5	3
Dithioglycolic acid	23	5
Thioglycolyloxalic acid	3	2
N-acetyl-S-cysteinyl acetyl derivative	50	28
N-acetyl-S-(2-carboxymethyl) cysteine	4	0
Urea	3	3.5

Based on Jones and Hathway, 1978b.

Table III-10

Effects of Inducers and Inhibitors of Microsomal Enzymes on Rate of Metabolism of 1,1-DCE

Chemical	Experimental Method	Metabolism	Investigator
CCl_4	whole animal	decrease	a
Pyrazole	whole animal	decrease	a
Aminotriazole	whole animal	decrease	a
2,3-Epoxypropan-1-ol	whole animal	none	a
Phenobarbital	whole animal	none	a
Phenobarbital	isolated perfused liver	increase	b
SKF 525-A	whole animal	none	a
SKF 525-A	isolated perfused liver	decrease	b
DDT	isolated perfused liver	increase	b
Decreased glutathione	isolated perfused liver	decrease	b

[a] Anderson _et al._, 1979b.

[b] Reichert and Henschler, 1978.
Reichert _et al._, 1978.

barbital and SKF 525-A, but these may be due to the difference in experimental technique, i.e., whole animal compared to isolated perfused liver.

Exposure of rats to trans-1,2-DCE or cis-1,2-DCE was shown to cause exhalation of acetone (Filser et al., 1978). However, this acetone is probably not a metabolite, but rather reflects a DCE-induced alteration in lipid and fatty acid metabolism.

Filser and Bolt (1980) studied this phenomenon further in adult male Wistar rats and concluded (based largely upon studies with the analog vinylidene fluoride) that the increased acetone expiration caused by inhalation of cis- or trans-1,2-dichloroethylene (110 to 135 ppm and 340 to 900 ppm, respectively) does not stem from the halocarbons themselves, but does require their biotransformation. This conclusion was based on the dependence of acetone production on vinylidene fluoride concentration, effects of agents which induce oxidative enzymes, effects of the metabolic inhibitor pyrazole, effect of cysteine, effect of hypoxia and the time course of acetone exhalation. Further, Filser, et al. (1982) showed that increased acetone exhalation also could be produced by administration of fluoroacetate or chloroacetate, a known metabolite of the dichloroethylenes. These haloacetates are effective inhibitors of the citric acid cycle and this mechanism is believed to be involved. However, the role of this process in the toxicity of the dichlorinated ethylenes is unclear.

Using isolated rat liver microsomes, both cis- and trans-1,2-DCE have shown competitive and reversible interaction with the mixed function oxygenase system. This interaction produced decreased drug metabolism (Freundt and Macholz, 1978).

Costa and Ivanetich (1982) have studied the biotransformation of both cis- and trans-1,2-dichloroethylene in vitro in rat liver microsomal preparations supplemented with NADPH. 2,2-Dichloroethanol and 2,2-dichloroacetic acid were formed, presumably by subsequent reduction or oxidation of 2,2-dichloroacetaldehyde. Treatment of rats with either phenobarbital or β-naphthoflavone increased the microsomal formation of 2,2-dichloroacetaldehyde from either cis- or trans-1,2-dichloroethylene.

D. Excretion

Considerable work on the excretion of 1,1-DCE and its metabolites has been done using [^{14}C]1,1-DCE (Jaeger et al., 1977a; McKenna et al., 1977, 1978a, 1978b; Jones and Hathway, 1978a; Reichert and Werner, 1978; Reichert et al., 1979). These data are summarized in Table III-6. The data show that both unmetabolized 1,1-DCE and CO_2 formed by biotransformation of 1,1-DCE are excreted via the lung, whereas the other metabolites are eliminated via renal and biliary excretion. However, the pattern of excretion depends upon the concentration of 1,1-DCE in the blood, which is affected by the amount of chemical administered and to a certain extent by the route of administration. At low dose levels where the concentration of 1,1-DCE in the blood is low and biotransformation is effective, most of the ^{14}C is eliminated as metabolites via renal and biliary excretion. It has been shown that a portion of the material excreted in the urine was actually of biliary origin and entered the urine by means of enterohepatic circulation (Jones and Hathway, 1978a). At higher dose levels where the concentration of 1,1-DCE in blood is much higher, biotransformation approaches saturation and becomes less effective in removing the xenobiotic from the blood as it passes through the liver. As a result, increasing amounts of untransformed 1,1-DCE are eliminated through the lung. This is reflected in a change in the relative amounts of ^{14}C excreted as 1,1-DCE and CO_2 via the lung. Another example of the effect of biotransformation on the course of elimination is seen by comparing the excretion following a low dose (0.5 mg/kg) of 1,1-DCE administered intravenously with results following oral or intraperitoneal administration. Whereas oral administration presents 1,1-DCE to the liver for biotransformation prior to passing through the lung, intravenous administration allows systemic distribution of 1,1-DCE and each pass brings approximately 25% of the blood to the liver. Therefore, the excretion by the lung is much more important following intravenous administration; a large part of the ^{14}C is eliminated as untransformed 1,1-DCE via the lung, rather than being eliminated as metabolites via the renal and biliary routes.

For 1,1-DCE the rate of elimination is relatively rapid, since most of the total absorbed dose is eliminated in the first 24-72 hours after administration (Jaeger, et al., 1977; McKenna, et al., 1977, 1978a; Jones and Hathway, 1978a).

Disappearance of covalently bound metabolites of 1,1-DCE, measured as TCA-insoluble fractions, also appears to be fairly rapid with a reported half-life of 2-3 hours (Jaeger et al., 1977a).

No data concerning the excretion of cis- and trans-1,2-DCE are available presently.

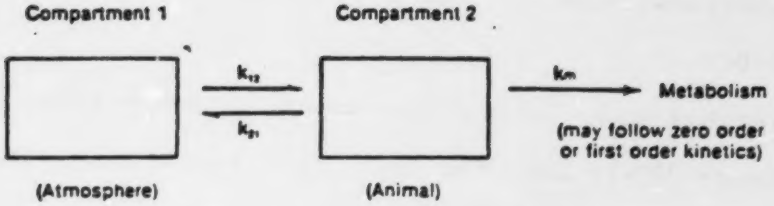
E. Kinetics

Several studies have shown that the kinetic behavior of the halogenated ethylenes is dose-dependent. This phenomenon is attributed to saturability of the biotransformation capacity of the organism at higher doses (Jones and Hathway, 1978a; McKenna *et al*., 1978a, 1978b; Reichert and Henschler, 1978; Reichert and Werner, 1978, Andersen *et al*., 1979a, 1979b, 1980a; Filser and Bolt, 1979). A hypothetical two compartment kinetic model (Figure III-4) has been employed to explain the results of inhalation studies of halogenated ethylenes (Filser and Bolt, 1979). In their closed system, saturation of the biotransformation processes was observed at high levels of exposure. When rats were exposed to atmospheric concentrations which exceeded the "point of saturation (SP)," biotransformation followed zero-order kinetics, i.e., the rate was independent of the concentration (Filser and Bolt, 1979). Concentrations below this saturation point resulted in normal first-order kinetics, i.e., the rate of biotransformation was dependent upon the concentration.

The transformation first-order clearance of the three dichloroethylenes is shown in Table III-11. Cis-1,2-DCE has the highest rate of clearance, trans-1,2-DCE the lowest and 1,1-DCE intermediate. The concentration of the dichloroethylenes in the air at which there is a transition from first-order to zero-order biotransformation also is shown in Table III-11. The concentration necessary to saturate biotransformation was much higher for 1,1-DCE than for the 1,2-DCEs. Although the *in vivo* transformation of DCEs does not follow simple Michaelis-Menten kinetics, a zero order kinetic rate con-

Figure III-4

Two Compartment Pharmacokinetic Model for DCEs Between a Closed Atmosphere and Animal and Metabolism


Compartment 1
Compartment 2
k_{12}
k_{21}
k_m
Metabolism
(may follow zero order or first order kinetics)
(Atmosphere)
(Animal)

Based on Filser and Bolt, 1979.

stant, V_{max}, for biotransformation under saturation conditions could be determined (Table III-11). This rate constant measures the maximum rate of biotransformation of a particular chemical. The V_{max} for 1,1-DCE is much higher than for the 1,2-DCEs. The V_{max} values are quite different for the isomeric DCEs even when a correction is made for the differing tissue concentrations of these materials. This suggests that the maximum velocity of biotransformation depends on the chemical structure. For the dichloroethylenes, the relative rate of biotransformation was determined to be 1,1-DCE > cis-1,2-DCE > trans-1,2-DCE.

A hypothetical three compartment, steady-state, kinetic model (Figure III-5) also has been used to explain kinetic data obtained in inhalation studies using gas uptake measurements (Andersen _et al_., 1980a, 1979a, 1979b). According to this model, tissues richly perfused with blood rapidly equilibrate with atmospheric vapors of the DCEs. Following the initial blood:gas equilibration, the blood concentration of DCEs is decreased by metabolism in the richly perfused tissues, storage in the poorly perfused tissues and excretion. Excretion of the untransformed volatile toxicants occurs primarily via the lungs into the expired breath. For both 1,1-DCE and trans-1,2-DCE, there were significant contributions to the overall gas uptake rate from both a first order process, k_{23}, representing storage in the poorly perfused tissues, and a saturable process, k_m, representing biotransformation. At very high concentrations, the relative contribution of the first order process (storage in poorly perfused tissue) to the overall gas uptake rate increased. At lower concentrations,

Table III-11

First-Order and Zero-Order Metabolic Elimination of DCEs from a Closed Exposure System: Saturation Points (Sp) and Metabolic Rates Expressed as V_{max} and Clearance, Based on 1 kg Body Weight

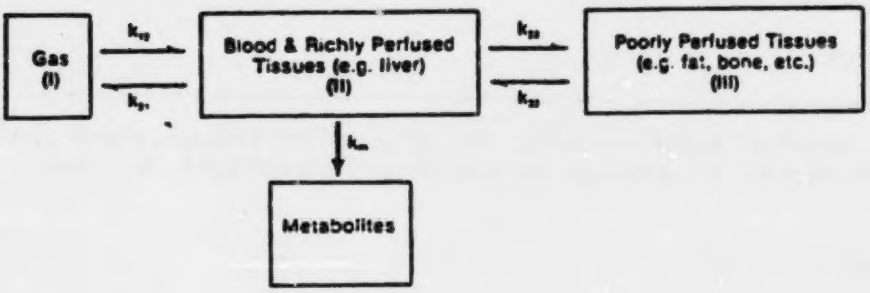
Chemical	First Order Clearance $\frac{\text{liter}}{\text{hr}\cdot\text{kg body weight}}$	Saturation Point, SP (ppm in air)	Zero Order V_{max} $\frac{\mu\text{mole}}{\text{hr}\cdot\text{kg body weight}}$
1,1-DCE	17	150	100
trans-1,2-DCE	11	(15)	7
cis-1,2-DCE	30	20	25

( ) Not observed experimentally, but obtained by extrapolation, i.e., from intersection of observed zero-order and first-order declines.

Filser and Bolt, 1979.

Figure III-5

Three Compartment Pharmacokinetic Model for Describing Uptake of DCEs by Rats


Gas
(I)
k_{12}
k_{21}
Blood & Richly Perfused Tissues (e.g. liver)
(II)
k_{23}
k_{32}
Poorly Perfused Tissues (e.g. fat, bone, etc.)
(III)
k_m
Metabolites

Based on Andersen et al., 1980a.

the first order process became less important and the saturable process (biotransformation) became the main route of gas uptake by the animal. Table III-12 contains the kinetic data determined for the saturable process. The concentration dependence of the saturable phase was adequately described by Michaelis-Menten kinetics. The V_{max}, the maximum rate of biotransformation, was determined to be 15.9 mg/kg·hr (164 umoles/kg·hr) for 1,1-DCE and 3.4 mg/kg·hr (35 umoles/kg·hr) for trans-1,2-DCE. Therefore, the relative rate of biotransformation was 1,1-DCE > trans-1,2-DCE. The atmospheric concentration, K_m, that causes transformation in vivo in rats to occur at one-half the maximum biotransformation rate also was determined. The K_m was found to be 336 ppm (55.1 umoles/liter plasma) for 1,1-DCE and 411 ppm (183 umoles/liter plasma) for trans-1,2-DCE.

Based on the analysis of the kinetics of DCE from the gas uptake studies, it has been suggested that the rate limiting step in biotransformation of DCEs at low concentration is blood flow to the liver (Andersen et al., 1980a). The rate at which an inhaled chemical is presented to the liver is determined by pulmonary absorption. Since the weight-adjusted breathing volume decreases as body weight increases, the rate of uptake and therefore the rate of presentation of DCEs to the liver would be expected to be reduced to a similar degree. For a rat, the resting breathing volume is estimated to be 32 liters/kg·hr. For a moderately active 70 kg human, the 8 hr work shift breathing volume is usually taken to be 10 m^3 i.e., 18 liters/kg·hr. Therefore, at lower exposure concentrations, less DCE would be presented to the liver in the human relative to rats. It has therefore been suggested that

Table III-12

Inhalation Kinetic Constants for the Metabolism of DCEs Determined Using Gas Uptake Measurements

	V_{max}[a]		K_m[b]	
Chemical	(mg/kg·hr)	(umoles/kg·hr)	(ppm)	(umoles/liter plasma)
1,1-DCE	15.9	164	336	55.1
trans-1,2-DCE	3.4	35	411	183

[a] V_{max} is the maximum rate of metabolism.

[b] K_m is the atmospheric concentration that causes metabolism *in vivo* to proceed at half maximal velocity.

Based on Andersen *et al.*, 1980a.

at low atmospheric concentrations, DCE biotransformation would be slower in the human than in the rat. This would shift the K_m (ppm in atmosphere) to even higher concentrations for the human (Andersen et al., 1980a), if V_{max} were similar in each species.

Assuming that biotransformation of 1,1-DCE is probably limited by hepatic perfusion and pulmonary ventilation at low inhaled concentrations, the relative amounts of metabolites formed by different species can be calculated. Humans, on a per unit weight basis, would biotransform considerably less 1,1-DCE to toxic metabolites than would the rat or mouse. The data for 1,1-DCE biotransformation in mice and rats in Table III-7 can be extrapolated by reference to physiologic parameters to yield an estimate of the amount of biotransformation likely to occur in a human exposed to 10 ppm of 1,1-DCE for six hours. Ventilation is given by an equation of the form (Guyton, 1947):

$$Vt = 0.126 \text{ l/hr (body weight)}^{0.75}$$

For the mouse, rat and human (30 g, 250 g and 70 kg, respectively), V is 53.0, 31.7 and 7.75 l/hr respectively, for the animals at rest. In a six-hour exposure to 10 ppm (0.0397 mg/l) each species will inhale 12.82, 7.55 and 1.65 mg/kg, respectively. The data in Table III-7, for the total transformed 1,1-DCE, show that the percent retained is 41% for the mouse and 38% for the rat. If the same percent retained (about 40%) holds, a human will biotransform only about 0.74 mg/kg. If these assumptions are correct, the human would biotransform about fourfold less than the rat (31.7/7.7 = 4.1) and about seven-fold less than the mouse (53.0/7.7= 6.9).

IV. HUMAN EXPOSURE

Humans may be exposed to 1,2-dichloroethylene in drinking water, food, and air. Detailed information concerning the occurrence of and exposure to 1,2-dichloroethylene in the environment is presented in another document entitled "Occurrence of 1,2-Dichloroethylene in Drinking Water, Food, and Air" (Letkiewicz et al. 1983). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food, and air.

Exposure Estimation

This analysis is limited to drinking water, food, and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to 1,2-dichloroethylene from sources other than the three considered here, notably in occupational settings and from the use of consumer products containing 1,2-dichloroethylene. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works, and travels, what one eats, and physiologic characteristics related to age, sex, and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various 1,2-dichloroethylene concentrations. The 70-kg male is used for estimating intake.

a. Water

Cumulative estimates of the U.S. populations exposed to various levels of cis- and trans-1,2-dichloroethylene in drinking water from public drinking water systems are presented in Table IV-I. The values in the table were obtained using Federal Reporting Data Systems data on populations served by

Table IV-I. Total Estimated Cumulative Population (in Thousands) Exposed to 1,2-Dichloroethylene in Drinking Water Exceeding the Indicated Concentration[a]

System type	Number of people served in U.S. (thousands)	Cumulative population (thousands) exposed to concentrations (ug/l) of:					
		≥ 0.5	> 5	> 10	> 20	> 30	> 40
Groundwater	73,473	2,934	477	352	352	176	0
Surface water	140,946	1,685	0	0	0	0	0
Total	214,419	4,619	477	352	352	176	0
(% of total)	(100%)	(2.2%)	(0.2%)	(0.2%)	(0.2%)	(0.1%)	(0.0%)

[a] Total estimated cumulatives are for total cis- and trans-1,2-dichloroethylene isomers.

primary water supply systems (FRDS 1983) and the estimated number of these water systems that contain a given level of 1,2-dichloroethylene. An estimated 4,619,000 individuals (2.2% of the population of 214,419,000 using public water supplies) are exposed to levels of 1,2-dichloroethylene in drinking water at or above 0.5 ug/l, while 477,000 individuals (0.2%) are exposed to levels above 5 ug/l. It is estimated that 176,000 individuals are exposed to levels greater than 30 ug/l. Of the approximately 4.1 million people exposed to levels ranging from 0.5 to 5 ug/l, 2.5 million (59%) obtain water from groundwater supplies. All exposure to 1,2-dichloroethylene in drinking water at levels above 5 ug/l is expected to be from groundwater sources.

No data were obtained on regional variations in the concentration of 1,2-dichloroethylene in drinking water. The highest concentrations are expected to occur near sites of production and use of 1,2-dichloroethylene.

Daily intake levels of 1,2-dichloroethylene from drinking water were estimated using various exposure levels and the assumptions presented in Table IV-II. The data in the table suggest that the majority of the persons using public drinking water supplies would be exposed to intake levels below 0.014 ug/kg/day.

Table IV-II. Estimated Drinking Water Intake of 1,2-Dichloroethylene

Exposure level (ug/l)	Persons using supplies exposed to indicated levels: Population	Persons using supplies exposed to indicated levels: % of Total population	Intake (ug/kg/day)
≥0.5	4,619,000	2.2%	≥0.014
>5.0	477,000	0.2%	>0.14
>10	352,000	0.2%	>0.29
>20	352,000	0.2%	>0.57
>40	0	0.0%	>1.1

[a] Estimated intake is for total cis- and trans-1,2-dichloroethylene isomers. Assumptions: 70-kg man, 2 liters of water/day.

An indication of the overall exposure of the total population to 1,2-dichloroethylene can be obtained through the calculation of population-concentration values. These values are a summation of the individual levels of 1,2-dichloroethylene to which each member of the population is exposed. An explanation of the derivation of these values is presented in Appendix C. Population-concentration estimates for 1,2-dichloroethylene in drinking water were 1.1×10^7 ug/l x persons (best case), 1.8×10^7 ug/l x persons (mean best case), 1.2×10^8 ug/l x persons (mean worst case), and 1.3×10^8 ug/l x persons (worst case).

Assuming a consumption rate of 2 liters of water/day, population-exposure values of 2.2×10^7 ug/day x persons (best case), 3.6×10^7 ug/day x persons (mean best case), 2.4×10^8 ug/day x persons (mean worst case), and 2.6×10^8 ug/day x persons (worst case) were derived.

b. Diet

No data were obtained on levels of 1,2-dichloroethylene in foods in the United States. Therefore, no estimates of the daily intake of 1,2-dichloroethylene from the diet could be made.

c. Air

Exposure to 1,2-dichloroethylene in the atmosphere varies from one location to another. The highest level of cis-1,2-dichloroethylene reported in the atmosphere was 27,000 ng/m^3 (27 ug/m^3) (Pellizzari et al. 1979 cited in Brodzinsky and Singh 1982). High levels, averaging greater than 3,000 ng/m^3 (3.0 ug/m^3), have been detected in other areas. Normal levels, however, are somewhat lower. Brodzinsky and Singh (1982) calculated median air levels of cis-1,2-dichloroethylene for rural/remote areas, urban/suburban areas, and source dominated areas of 0.0 ng/m^3 (0.0 ug/m^3), 270 ng/m^3 (0.27 ug/m^3), and 1,200 ng/m^3 (1.2 ug/m^3), respectively. trans-1,2-Dichloroethylene was monitored at only one site at a level of 3,700 ng/m^3 (3.7 ug/m^3) (Pellizzari 1978 cited in Brodzinsky and Singh 1982).

The monitoring data available are not sufficient to determine regional variations in exposure levels for 1,2-dichloroethylene. However, urban and industrial areas appear to contain higher levels, as expected.

The daily respiratory intake of cis-1,2-dichloroethylene from air was estimated using the assumptions presented in Table IV-III and the median and maximum levels for cis-1,2-dichloroethylene reported above. The estimates in Table IV-III indicate that the daily cis-1,2-dichloroethylene intake from air for adults in source dominated areas is approximately 0.4 ug/kg/day. In contrast, the intake calculated using the maximum level reported is 8.9 ug/kg/day; few if any persons are believed to be exposed at that level. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Table IV-III. Estimated Respiratory Intake of cis-1,2-Dichloroethylene

Exposure (ug/m^3)	Intake (ug/kg/day)
Rural/remote (0.0)	0.0
Urban/suburban (0.27)	0.089
Source dominated (1.2)	0.39
Maximum (27)	8.9

Assumptions: 70-kg man, 23 m^3 of air inhaled/day (ICRP 1975).

SUMMARY

Table IV-IV presents a general view of the total amount of 1,2-dichloroethylene received by an adult male from air and drinking water. Four separate exposure levels in air and six exposure levels in drinking water are shown in the table. No data were obtained on levels of 1,2-dichloroethylene in foods: therefore, the relative contribution of 1,2-dichloroethylene in the diet to total 1,2-dichloroethylene exposure could not be assessed.

It should be noted that the intake of 1,2-dichloroethylene from drinking water is based on data for both the cis and trans isomers, while the intake from ambient air is based on data for the cis isomer only. The intake of 1,2-dichloroethylene from ambient air would be expected to be somewhat higher if both isomers were accounted for.

The data presented have been selected from an infinite number of possible combinations of concentrations for the two sources. The actual exposures encountered would represent some finite subset of this infinite series of combinations. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to 1,2-dichloroethylene at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of 1,2-dichloroethylene of 0.27 ug/m^3 based on air monitoring data. Assuming an air level of 0.27 ug/m^3, drinking water would be the predominant source of 1,2-dichloroethylene exposure in the adult male at drinking water levels above 3.1 ug/l. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of 1,2-dichloroethylene in drinking water and low concentrations of 1,2-dichloroethylene in ambient air and food are unknown.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for 1,2-dichloroethylene by route of exposure. The relative dose received may vary from the relative intake. In addition, the relative effects of the chemical on the body may vary by different routes of exposure.

Table IV-IV. Estimated Intake of 1,2-Dichloroethylene from the Environment by Adult Males in ug/kg/day (% from Drinking Water)[a]

Concentration in drinking water (ug/l)	Concentration in air			
	Rural/remote ($0.0\ ug/m^3$)	Urban/suburban ($0.27\ ug/m^3$)	Source dominated ($1.2\ ug/m^3$)	Maximum ($27\ ug/m^3$)
0	0.0 (--)	0.089 (0%)	0.39 (0%)	8.9 (0%)
0.5[b]	0.014 (100%)	0.10 (14%)	0.40 (3.5%)	8.9 (0.16%)
5.0[c]	0.14 (100%)	0.23 (61%)	0.53 (26%)	9.0 (1.6%)
10[d]	0.29 (100%)	0.38 (76%)	0.68 (43%)	9.2 (3.2%)
20[e]	0.57 (100%)	0.66 (86%)	0.96 (59%)	9.5 (6.0%)
40[f]	1.1 (100%)	1.2 (92%)	1.5 (73%)	10 (11%)

Intake from each source:

Water:	0.5 ug/l:	0.014 ug/kg/day
	5.0 ug/l:	0.14 ug/kg/day
	10 ug/l:	0.29 ug/kg/day
	20 ug/l:	0.57 ug/kg/day
	40 ug/l:	1.1 ug/kg/day
Air:	$0.27\ ug/m^3$:	0.089 ug/kg/day
	$1.2\ ug/m^3$:	0.39 ug/kg/day
	$27\ ug/m^3$:	8.9 ug/kg/day
Food:	Not included	

[a] Estimated intake is for total cis- and trans-1,2-dichloroethylene isomers.

[b] 4,619,000 individuals using public drinking water systems are estimated to be exposed to levels ≥ 0.5 ug/l (2.2% of population using public water supplies).

[c] 477,000 individuals using public drinking water systems are estimated to be exposed to levels > 5.0 ug/l (0.2% of population using public water supplies).

[d] 352,000 individuals using public drinking water systems are estimated to be exposed to levels > 10 ug/l (0.2% of population using public water supplies).

[e] 352,000 individuals using public drinking water systems are estimated to be exposed to levels > 20 ug/l (0.2% of population using public water supplies).

[f] No individuals using public drinking water systems are estimated to be exposed to levels > 40 ug/l.

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V. HEALTH EFFECTS IN ANIMALS

A. Acute and Chronic Effects

Data on the acute oral toxicity of the DCEs in laboratory animals, as measured by the LD_{50}, have been reported in several studies (Jenkins *et al.*, 1972; Andersen and Jenkins, 1977b; Freundt *et al.*, 1977; Jones and Hathway, 1978b; NIOSH, 1978; Andersen *et al.*, 1979a; Ponomarkov and Tomatis, 1980). Data from these sources are summarized in Table V-1. These data show a wide range of values for the LD_{50}.

The use of different vehicles may account partially for the wide range of LD_{50} values reported in Table V-1. Chieco, *et al.*, (1981) noted considerable variation in the acute effects of 1,1-dichloroethylene as a function of feeding status and the vehicle of administration. Fasted animals were considerably more sensitive than were fed animals. Further, acute toxicity was considerably more severe in rats given 1,1-dichloroethylene in corn oil or mineral oil than in Tween 80. The difference among effects of the vehicles could not be attributed to either the rate of fast-phase exhalation of 1,1-dichloroethylene or the total amount of 1,1-dichloroethylene exhaled or to the ability of the animals to detoxicate the agent.

1,1-Dichloroethylene. The lethality of 1,1-DCE in fasted rats was found to depend upon the size (age) of the animals: large rats (395 g) had an oral LD_{50} (observed for 14 days following dosage) of > 1500 mg/kg, whereas smaller (73 g) rats had an LD_{50} of <100 mg/kg (Andersen and Jenkins, 1977b). The LD_{50} value for the larger rats agreed with a previous study (Jenkins *et al.*, 1972). The dose mortality curves for the fasted rats showed an

Table V-1

Acute Toxic Effects of DCEs

Compound	Route	Species	Dose	Effect	Reference
1,1-DCE	oral	rat	200 mg/kg	LD_{50}	NIOSH (1978)
1,1-DCE	oral	rat rat^{a}	>1500 mg/kg 84 mg/kg	LD_{50} LD_{50}	Jenkins, *et al*. (1972) Jenkins, *et al*. (1972)
1,1-DCE	oral	rat (395 g) (fasted)	>1500 mg/kg	LD_{50}	Andersen and Jenkins (1977b)
1,1-DCE	oral	rat (138 g) (fasted)	<50 mg/kg	LD_{50}	Andersen and Jenkins (1977b)
1,1-DCE	oral	rat (Male) rat (Female)	1800 mg/kg 1500 mg/kg		Ponomarkov and Tomatis (1980)
1,1-DCE	oral	mouse (male)	217 mg/kg	LD_{50}	Jones and Hathway (1978b)
		mouse (female)	194 mg/kg		Jones and Hathway (1978b)
1,1-DCE	oral iv	dog dog	5750 mg/kg 225 mg/kg	LD_{50} LD_{50}	NIOSH (1978) NIOSH (1978)
1,1-DCE	inhal	rat (fed)	15,000 ppm/4 hr	LC_{50}	Jaeger *et al*. (1974)
	inhal	rat (fasted)	600 ppm/4 hr	LC_{50}	Jaeger *et al*. (1974)
	inhal	rat (fasted)	200 ppm/4.1 hr 400 ppm/3.6 hr 500 ppm/13.0 hr 1000 ppm/2.4 hr 2000 ppm/1.4 hr	LC_{50}	Andersen *et al*. (1979a)
1,1-DCE	inhal	rat (fed)	6350 ppm/4 hr	LC_{50}	Siegel *et al* (1971)

Table V-1 (Continued)

Compound	Route	Species	Dose	Effect	Reference
1,2-DCE	oral	rat	770 mg/kg	LD_{50}	NIOSH (1978)
	ip	mouse	2000 mg/kg	LD_{50}	NIOSH (1978)
trans, 1-2-DCE	oral	rat (180-200 g)	1.0 ml/kg (1300 mg/kg)	LD_{50}	Freundt *et al.* (1977)
	ip	rat (180-200 g)	6.0 ml/kg (7800 mg/kg)	LD_{50}	Freundt *et al.* (1977)
	ip	mouse	3.2 ml/kg (4160 mg/kg)	LD_{50}	Freundt *et al.* (1977)

[a] Adrenalectomized

extended plateau and even a maximum that reached 100% and then decreased at higher doses for young animals (73 g). Because of this unusual dose-response, the authors concluded that it was impossible to unambiguously determine LD_{50} values for 1,1-DCE in younger rats (Andersen and Jenkins, 1977b). It also was determined in this study that the amount of 1,1-DCE retained by immature fasted male rats increased linearly up to a total dose of 100 mg/kg and then leveled off due to the greater percentage of the dose being excreted by the lungs at higher doses (Andersen and Jenkins, 1977b).

The acute inhalation toxicity of 1,1-DCE also has been determined (Jaeger et al., 1974). A large difference in 24-hr LC_{50} values was found between fed (15,000 ppm) and fasted (600 ppm) rats exposed for four hours. In another study of the inhalation toxicity of 1,1-DCE in mature male rats, the percent mortality that occurred in a 7-day 4-hr exposure increased from 0 to 50% in the concentration range from 100 to 200 ppm but did not increase much over 50% as the concentration was increased from 200 to 2000 ppm, i.e., mortality was virtually independent of concentration (Andersen et al., 1979a). At high concentrations, the mortality was related to the duration of exposure rather than to the ambient concentration.

Based on the above data for the acute oral and inhalational toxicity, it has been suggested that the acute toxicity of 1,1-DCE is the result of a toxic metabolite and not due to the parent compound. Further, this metabolite is formed by a saturable process (Andersen et al., 1979a, 1980b). Under inhalation exposure conditions above the point of saturation of biotransformation, i.e., ambient concentrations above the 200 ppm, untransformed 1,1-DCE is readily excreted via the lung. Using data from kinetic studies on the biotransformation rate, the acute inhalation toxicity in rats was shown to be a function of the amount of metabolite formed and not of the concentration of 1,1-DCE (Andersen _et_ _al_., 1979b). Short term exposures produced mortality after formation of 25-30 mg of metabolite/kg. At concentrations between 200-1000 ppm, a direct correspondence was found between the duration of an exposure required to kill rats (LT_{50}) and the time calculated to produce a constant amount of metabolite (Andersen _et_ _al_., 1979b)

A comparative study of the lethality of 1,1-DCE in different species showed that inhalation of 60 ppm of 1,1-DCE for 2 days caused higher mortality in mice (8/10) than in rats (0/10) (Short _et_ _al_., 1977a). This study also showed that there were similar values for the LC_{50} for one-day exposures (22-23 hrs/day) to 1,1-DCE in male (98 ppm) and female (105 ppm) mice. After repeated exposures, male mice were more sensitive to the lethal effects of 40 ppm of 1,1-DCE since the mortality for males after day 3 (3/10) and day 5 (7/10) of exposure was higher than for females (0/10). Similarly, it has been shown that species, strain and sex greatly influence the toxic effects of 1,1-DCE, presumably due to the formation of differing amounts of toxic metabolites (Maltoni, 1977).

The effects of exposure to 1,1-DCE over a greater number of days also have been studied. Repeated exposure (20 days) of rats to 500 ppm of 1,1-DCE for 6 hr/day has been reported to cause nasal irritation, decreased body weight gain and liver cell degeneration, whereas only slight nasal irritation was noted for the same exposures to 200 ppm (Gage, 1970).

It also has been reported that liver and kidney damage occurred in animals exposed by inhalation for 8 hr/day, 5 day/week for several months at concentrations of 50 and 100 ppm of 1,1-DCE in air (Irish, 1963).

Continuous 90-day inhalation exposures to 0, 5, 15, 25 or 47 ppm (0, 20, 61, 101 or 189 mg/m^3) of 1,1-DCE or repeated daily exposures of 8 hr/day, five days per week for six weeks to 100 ppm (395 mg/m^3) were studied using rats, guinea pigs, dogs, rabbits and monkeys (Prendergast, et al., 1967). Repeated exposures (30 exposures) to 100 ppm produced no mortality or visible toxic signs in any species. Hematologic and growth data did not reveal any evidence of a toxic response and histopathologic findings were negative in all species. In contrast to repeated intermittent exposures, continual exposure to 1,1-DCE caused increased mortality at concentrations as low as 5 ppm for guinea pigs and 25 ppm for monkeys. Growth depression was found in all species at the 47 ppm exposure level. Significant increases in serum glutamic-pyruvic transaminase and liver alkaline phosphatase were found in rats and guinea pigs exposed continually to the 47 ppm level, but these changes could not be demonstrated at the 5 ppm level. No determinations of enzyme levels were performed at the 15 and 25 ppm levels. Histopathological study of organs revealed definite morphological changes in liver and kidneys of rats and guinea pigs at the 47 ppm exposure level, but none at 25 ppm or lower.

concentration, total and differential white cell counts. Urinalyses to measure specific gravity, sugar, protein, ketones, occult blood, bilirubin and a microscopic examination of sediment were conducted on day 83 and at necropsy. Clinical chemistry, done after overnight fasting on days -7, +85 and +97, included blood urea nitrogen, serum GPT, alkaline phosphatase, serum GOT. Non-protein free SH content of liver and kidney was determined at necropsy, along with weights of the brain, liver, kidney, heart and testes, following overnight deprivation of food. Ophthalmological exams were conducted on all animals at the start and end of the study. At necropsy, both eyes of each dog in the control and high dose groups were examined grossly and microscopically.

No exposure-related changes were observed in appearance, demeanor, body weights or food consumption. The mean white cell counts of dogs receiving 6.25 or 25 mg/kg/day were significantly lower than control values on day 84 ($P<0.05$). However, these values were not significantly different from their own pre-exposure white cell counts. In addition, they were within the range of normal values observed in that laboratory. Therefore, the investigators considered the differences to be unrelated to the ingestion of 1,1-DCE.

Female dogs receiving 6.25 mg/kg 1,1-DCE exhibited a statistically significant decrease in BUN levels at day -7 and increase in SGPT at day 85 (38 ± 7 in controls vs. 50 ± 6 in treated; $P<0.05$). Males in that dose group showed elevated SGOT and SGPT at sacrifice ($P<0.005$). These comparisons were made with the concomitant controls. However, the investigators stated that the values were within the range of normal values observed historically in that laboratory. No alterations in the clinical chemistry parameters were noted at the 12.5 or 25 mg/kg/day doses except for one high dose male that had an elevated SGPT on day 85 but not on day 97. No changes were seen in the SH content of the liver or kidneys.

No compound-related changes were reported in any of the parameters measured on urinalysis, in organ weight or organ:body weight ratios or on gross or microscopic examination of tissues. One male receiving 12.5 mg/kg/day had grossly enlarged kidneys, but no accompanying histopathology. The investigators concluded that this finding was not compound-related.

Results were reported from a 90-day toxicity study in rats given nominal concentrations of 50, 100 or 200 ppm of 1,1-DCE in water or exposed for 6 hr/day, 5 days/week at initial levels of 0, 10 or 40 ppm 1,1-DCE in air (Rampy, et al., 1977). After 5 weeks, the doses were increased to 25 or 75 ppm. There was also a separate study done at 0, 25 or 75 ppm.

Ten rats/sex/group were used, with 2 rats/sex/group sacrificed at days 1,3,10 and 30 for the determination of non-protein sulfhydryl groups in the liver and kidney. The mean daily dosage levels in mg/kg based upon the amount of water consumed were 0, 7.5, 12.6 or 25.6 mg/kg for the females and 0, 5.9, 10 or 19 mg/kg for the males. Body weight was recorded once a week for the first month and monthly thereafter. Hematological and clinical chemistry measurements and urinalyses were conducted at 30 and 90 days. The parameters measured were the same as described in Ouast, et al.(1983).

Except for a decreased kidney:body weight ratio in males at the low dose, there were no statistically significant differences in organ weights or organ:body weight ratios at the termination of the study. The only histopathology noted was an increased cytoplasmic vacuolization of hepatocytes in livers of both sexes exposed to the highest dose. The investigators considered this to be a minimal change which would be reversible if the animals were removed from exposure to the chemical.

In the inhalation studies, there were no significant differences in organ weights at 30 or 90 days. Increased vacuolization in the liver was seen at both the 25 and 75 ppm exposure levels at 30 days and beyond. It was not seen in rats exposed to 10 or 40 ppm for only 30 days.

A two year chronic toxicity/oncogenicity study was conducted in rats given nominal concentrations of 0, 50, 100 or 200 ppm of 1,1-DCE in drinking water (Rampy, et al.,1977; Ouast, et al., 1983). In the interim report, the primary finding from this study was increased vacuolization of hepatocytes in the livers in the of animals in the high dose group (Rampy et al., 1977). Based on gross tumor count, tumor incidence was not greater than controls.

The time-weighted average mg/kg/day doses were 0, 7, 10 or 20 for the males and 0, 9, 14 or 20 for the females. Groups of 48 animals/sex/dose were used, except for controls (80/sex). The animals were observed at least twice a week for overt toxicity, changes in appearance or behavior and tumor formation. Biweekly food consumption and daily water consumption were measured for the first three months; these determinations were made at periodic intervals thereafter. Body weights were recorded once a week for 14 weeks and monthly thereafter. Hematologic determinations and urinalyses were conducted on at least 5 rats/sex/group at 6, 12, 18 and 23 months. Clinical chemistry measurements were made on 5 rats/sex/group at 6, 12 and 18 months and on 10 rats/sex/group or all survivors if fewer than 10 remained at terminal necropsy. The parameters measured are the same as those described above for the subchronic rat study (Rampy, et al., 1977).

At necropsy, following overnight fasting, the brain, heart, liver, kidney and testes were weighed. Gross and microscopic examination was done on complete sets of tissues (37) on all control and high dose animals. Only selected tissues from target organs and grossly recognizable neoplastic changes were examined microscopically from animals at the other two dose levels.

No consistent, dose-related changes were observed in any parameter measured. The only pathological finding considered by the investigators to be treatment-related was in the liver of animals of both sexes in the high-dose group. These microscopic changes, when present, were usually characterized by a minimal amount of mid-zonal hepatocellular fatty change. The degree of increase in this pathology was statistically significant in the males. A trend toward this increase was seen in males at the intermediate dose. No exposure-related changes were seen in males at the low dose. Minimal hepatocellular swelling and fatty changes were detected in female rats at all dose levels.

No significant treatment-related hepatocellular necrosis was evident in either sex at any dose.

Cis- and trans-1,2-dichloroethylene. The LD_{50} values for 1,2-DCE (isomer mixture) and trans-1,2-DCE are shown in Table V-1 (Freundt, et al., 1977). No similar data are available for the cis- isomer.

The effects of short- and long-term inhalation exposure to trans-1,2-DCE have been investigated (Freundt, et al.,1977). Adult female rats were exposed to 0, 200, 600 or 1000 ppm trans-1,2-DCE for 8 hr/day, 5 days/week for 16 weeks. The lowest dose produced histological evidence of slight to severe fatty degeneration of liver lobules and Kupffer cells. In addition, marked pulmonary hyperemia and alveolar septal distension were noted. Fibrous swelling of cardiac muscle also was observed. Exposure to 1,000 ppm of trans-1,2-DCE for 8 hours caused a fall in blood serum albumin, urea nitrogen, alkaline phosphatase activity and number of erythrocytes while 200 ppm for 8 hours was sufficient to lower leukocyte count. All of the exposure conditions investigated failed to produce narcosis.

B. Specific Toxic Effects

1. Liver

The most common toxic effect of 1,1-DCE is liver damage, which has been documented in rats, mice and guinea pigs. The morphological changes appear in fasted rats as early as 2 hr after the start of inhalation exposure to 200 ppm of 1,1-DCE (Reynolds, et al., 1975). The parenchymal cell injury is characterized by the retraction of cell borders with the formation of pericellular "lacunae" which may contain cytoplasmic projections, red blood cells and fibrin. Nuclear changes include loss of perinuclear chromatin and clumping and coalescence of perinuclear chromatin. Mitochondria in the cytoplasm appear swollen, with ruptured outer membranes. The rough and smooth endoplasmic reticulum appear relatively normal. The zone of injured midzonal parenchymal cells becomes confluent, forming a prominent midzonal stripe of necrosis which leads to hemorrhagic centrilobular necrosis. In contrast to damage caused by 1,1-DCE, the morphological change in liver caused by exposure to other halogenated ethylenes characteristically is damage to the endoplasmic reticulum. This suggests a basic difference in the mechanisms of toxicity of 1,1-DCE (Reynolds et al., 1975).

Hepatotoxicity of 1,1-DCE has been shown to have a complex dose-dependent response, having a threshold level, a concentration range of rapid increase, and an extended plateau where increasing doses caused little increase in hepatotoxicity. The threshold was lower for male rats (50 mg/kg) than for female rats (100 mg/kg) (Andersen and Jenkins, 1977b).

Continual exposure of rats or guinea pigs to 47 ppm of 1,1-DCE for 90 days caused significant increases in serum glutamic-pyruvic transaminase and liver alkaline phosphatase activities, but these changes could not be demonstrated at the 5 ppm level. Although no determinations of enzyme levels were performed at the 15 and 25 ppm levels, histopathological study of organs revealed definite morphological changes in liver and kidneys of rats and guinea pigs at the 47 ppm exposure level, but not at 25 ppm or lower (Prendergast et al., 1967). Oral administration of a single dose of 500 mg/kg of 1,1-DCE decreased liver glucose-6-phosphatase, but increased liver alkaline phosphatase (5-fold increase), liver tyrosine transaminase (11-fold increase), plasma alkaline phosphatase and plasma alanine transaminase (Jenkins et al., 1972). Exposure of rats to 60 ppm of 1,1-DCE for 22 hr/day for 7 days caused increased levels of both serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase (Short et al., 1977a).

Fasted rats were found to be more sensitive to both lethal and hepatotoxic effects of 1,1-DCE. An increase in serum alanine alpha-ketoglutarate transaminase (AKT) level was observed at 24 hours after a 4 hr exposure to 150 ppm in fasted rats, whereas a similar increase was observed in fed rats only at 2000 ppm or higher. Elevated serum AKT preceded hepatic necrosis and death. This fed-fasted difference in serum AKT elevation also was observed in isolated perfused rat liver (Jaeger et al., 1974). The increased susceptibility to liver injury has been attributed to decreased hepatic glutathione concentration which occurs after fasting (Jaeger et al., 1974, 1975a), after administration of some chemicals, e.g., diethyl maleate (Jaeger et al., 1974) or as a result of normal diurnal variation (Jaeger et al., 1973a). Additional evidence concerning the importance of glutathione concentration is the observation that thyroidectomy, which causes an increase in glutathione level, protects against hepatic injury and mortality from 1,1-DCE (Szabo et al., 1977). Conversely, pretreatment of animals with thyroxine was found to cause depletion of glutathione and increased hepatotoxicity (Jaeger et al., 1977b).

With regard to the difference in hepatotoxicity between fed and fasted rats, an in vitro study has shown that the activity of the enzymes of the mixed function oxidase system is greatly enhanced in fasted rats, without a significant increase in the microsomal protein and cytochrome P-450 content. The in vitro rate of transformation of 1,1-DCE using microsomes obtained from fasted rats was double the rate of microsomes from fed rats, suggesting that formation of increased amounts of metabolite may be responsible for the increased hepatotoxicity of 1,1-DCE in fasted rats (Nakajima and Sato, 1979).

The glutathione level of the liver was shown to be decreased greatly following a 4 hour exposure of rats to 200 or 2000 ppm of 1,1-DCE and to rebound to higher than normal levels 24 hours after the end of the exposure (Jaeger et al., 1973a; Reynolds et al., 1975). However, the glutathione level in the mitochondria was shown to remain depressed for 24 hours following exposure. Decreased uptake of O_2 by mitochondria isolated from rats exposed to 1,1-DCE paralleled the decrease in glutathione in the mitochondria. Additionally, the serum levels of sorbitol dehydrogenase, an enzyme of cytoplasmic origin, and carbamyl transferase, an enzyme of mitochondrial origin, were elevated concurrently. Both glutathione depletion and reduced O_2 uptake were shown to occur before serum enzyme levels increased. An increase in total liver citric acid level also was found. Based on these observations, it has been suggested that 1,1-DCE may be oxidized by the mixed function oxidases to monochloroacetic acid which is transformed further to a material, possibly monochlorocitric acid, that inhibits mitochondrial performance. This mitochondrial injury may be the basis for the hepatotoxicity (Jaeger, 1977). Histochemical work has shown that exposure to 1,1-DCE caused a dramatic alteration in the pattern and a reduced intensity of the mitochondrial membrane markers, monoamine oxidase and succinate dehydrogenase. These results were interpreted as suggesting the mitochondrial membrane as a major focus of injury (Chieco *et al.*, 1979).

Further studies by Reynolds and his colleagues have shown that exposure of fasted male Sprague-Dawley rats (150-200 g) to 200 ppm 1,1-dichloroethylene by inhalation for 1-4 hours resulted in a number of changes. Intracellular sodium levels began to rise during the first hour and preceded the morphologically apparent injury (Reynolds, *et al.*, 1980). In another study in which similar animals were given oral doses of 200 mg of 1,1-dichloroethylene per kg, the same effect was observed, and, in addition, striking decreases were observed in the centrilobular staining patterns of bile canaliculi membrane Mg^{+2}-ATPase, outer mitochondrial monoamine oxidase and inner mitochondrial membrane succinate dehydrogenase and cytochrome oxidase (Chieco, *et al.*, 1982). Six hours later, responses included decreases in cytochrome P-450, declines in mitochondrial K^{+}, marked imbalances in mitochondrial Na^{+}, Zn^{+2} and Mg^{+2} ion concentrations, increased serum transaminase activities, Ca^{+2} influx into cells and decreased staining of other plasma membrane and mitochondrial membrane components. From these studies, the authors concluded that plasma membranes and mitochondrial membranes appear to be the primary foci of injury.

While 1,1-dichloroethylene administration has been shown clearly to decrease glutathione levels in vivo, a single relatively high oral dose of 1,1-dichloroethylene (500 mg/kg po in corn oil) did not significantly ($P > 0.05$) decrease levels of the glucuronidation cofactor uridine diphosphate glucuronic acid in livers of seven fasted adult male Sprague-Dawley rats (Watkins and Klaassen, 1983).

The role of lipid peroxidation in hepatotoxicity by 1,1-DCE has been investigated. Whereas one study concluded that lipid peroxidation was not the mechanism of hepatic injury by 1,1-DCE (Jaeger et al., 1973b), another study showed that depletion of glutathione in the liver by 1,1-DCE caused an increase in spontaneous lipid peroxidation (Younes and Siegers, 1980).

The relationship of the biotransformation of the DCEs to their toxicity is not well understood. The effects of inducers and inhibitors of microsomal enzymes and xenobiotic substrates which would compete for biotransformation with DCEs have been investigated. Table V-2 summarizes the results obtained as measured by lethality, hepatotoxicity and metabolic rates. The data demonstrate that conflicting results were obtained in different studies with inducers and inhibitors of microsomal enzymes. It has been shown that the response of rats to a particular material depends upon the age or body weight (Andersen et al., 1978). Whether or not this accounts for the different response between studies is uncertain. It has been suggested that the pretreatments may interact with different sequential steps of a multi-step metabolic pathway or with different metabolic pathways (Andersen et al., 1978). An alternative pro-

Table V-2

Result of Various Pretreatments on 1,1-DCE Effects in Rats

Pretreatment	Lethality	Hepatotoxicity	Metabolism	Reference
Microsomal Inducers				
Phenobarbital		decrease		Reynolds et al., 1975, 1977
Phenobarbital	increase	no change		Carlson and Fuller, 1972
Phenobarbital		decrease		Jenkins et al., 1972
Phenobarbital	decrease^a increase^b		no change	Andersen et al., 1978, 1979b
Phenobarbital			10% increase	Reichert and Henschler, 1978
3-Methylcholanthrene		no change		Reynolds et al., 1975, 1977
3-Methylcholanthrene	increase	no change		Carlson and Fuller, 1972
Aroclor 1254		decrease		Reynolds et al., 1975, 1977
Hexachlorobenzene		no change		Reynolds et al., 1975, 1977
DDT			35% increase	Reichert and Henschler, 1978
Spironolactone		no change		Reynolds et al., 1975, 1977
Pregnenolone-16-carbonitrile		no change		Reynolds et al., 1975, 1977
Microsomal Inhibitors				
SKF 525-A	no change^a increase^b		no change	Andersen et al., 1978, 1979b
SKF 525-A	increase	no change		Carlson and Fuller, 1972
SKF 525-A			decrease	Reichert and Henschler, 1978
SKF 525-A	no change	no change		Jaeger et al., 1975b
Pyrazole	decrease^c		84% decrease	Andersen et al, 1978, 1979b
3-Aminotriazole	decrease^c		65% decrease	Andersen et al., 1978, 1979b
CCl_4	decrease		92% decrease	Andersen et al., 1978, 1979b
Diethyl Dithiocarbamate	decrease	decrease		Short et al., 1977a, 1977b
Diethyl Dithiocarbamate		decrease	decrease	Siegers et al., 1979
Disulfiram	decrease	decrease		Short et al., 1977a, 1977b
Thiram	decrease	decrease		Short et al., 1977a, 1977b

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[a] Small rats
[b] Large rats
[c] Rats of various sizes

continued-

Table V-2. Result of Various Pretreatments on 1,1-DCE Effects in Rats (Continued)

Pretreatment	Lethality	Hepatotoxicity	Metabolism	Reference
Competitive Substrates				
2,3-Epoxypropan-1-ol	increase		no change	Andersen *et al.*, 1977a, 1979b
Epichlorohydrin	increase			Andersen *et al.*, 1980b
Styrene oxide	increase		decrease	Andersen *et al.*, 1980b
Butadiene monoxide	increase		decrease	Andersen *et al.*, 1980b
Competitive Substrates				
Cyclohexene oxide	increase		decrease	Andersen *et al.*, 1980b
Diethyl maleate	increase		decrease	Andersen *et al.*, 1980b
Cysteine	decrease	decrease		Jaeger *et al.*, 1975b
Cysteine	decrease			Short *et al.*, 1977b
Methionine	decrease			Short *et al.*, 1977b
N-Acetyl cysteine	no change			Short *et al.*, 1977b
Vitamin C	no change			Short *et al.*, 1977b
Vitamin E	no change			Short *et al.*, 1977b
Vinyl Chloride[d]		decrease	no change	Jaeger *et al.*, 1975a
Free Radical Scavenger				
(+) Cyanindol-3		decrease	no change	Siegers *et al.*, 1979

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[d] Administered simultaneously, not as a pretreatment

posal has been made that different mechanisms may be responsible for lethality and hepatotoxicity (Reynolds and Moslen, 1977). However, one can conclude that the microsomal enzyme inducers did not potentiate markedly the hepatotoxic effects of 1,1-DCE as they do for many other halogenated hydrocarbons. This lack of effect might be because the biotransformation of 1,1-DCE is blood flow limited (Andersen et al., 1980a).

The classical microsomal enzyme inhibitor, SKF 525-A, does not alter the hepatotoxic effects of 1,1-DCE but does increase the lethality at least in larger rats. Also, it has been reported that pretreatment of rats with disulfiram or diethyl dithiocarbamate reduces lethality, hepatotoxicity and the amount of covalently bound ^{14}C in livers of mice exposed to $[^{14}C]$1,1-DCE (Short et al., 1977a,b; Siegers et al., 1979). Disulfiram is known to reduce hepatic cytochrome P-450 levels. However, it is also readily split into diethyl dithiocarbamate which has sulfhydryl groups that can react with toxic metabolites (Bartsch et al., 1979). This may be the mechanism by which it decreases hepatotoxicity. Similarly, cysteine and methionine have been shown to reduce the lethality and hepatotoxicity (Jaeger et al., 1975b; Short et al., 1977b). Pretreatment with epoxides, which would interfere with subsequent biotransformation of a toxic electrophilic intermediate, has been shown to increase hepatotoxicity (Andersen et al., 1980b). Simultaneous administration of vinyl chloride causes a decrease in hepatotoxicity, presumably by competing with 1,1-DCE for reaction with the mixed function oxidases (MFOs) (Jaeger et al., 1975a). Pretreatment with antioxidants such as vitamin C or vitamin E had no effect on lethality (Short et al., 1977b).

The hepatotoxicity of 1,2-DCE, as determined by changes in hepatic enzymes, was studied and cis-1,2-DCE was found to be slightly more hepatotoxic than trans-1,2-DCE but both had less effect on the liver than 1,1-DCE (Jenkins et al., 1972). It has been reported that repeated inhalation exposures of rats to 200 ppm of trans-1,2-DCE for 8 hr/day, 5 days/week for 16 weeks produced fatty degeneration of the liver lobules and Kupffer cells (Freundt et al., 1977).

2. Kidney

Although renal lesions have been demonstrated histologically in studies at doses of 1,1-DCE similar to those causing hepatotoxicity, there has been limited research on this topic (Prendergast et al., 1967; Short et al., 1977a,b). The nephrotoxic effects of a single oral dose of 200, 400 or 600 mg/kg of 1,1-DCE have been examined in rats. Increases in plasma urea nitrogen and plasma creatinine levels as well as increased kidney weight were found in males but not in females. However, both sexes showed similar histopathologic changes: vacuolization, tubular dilatation and necrosis (Jenkins and Andersen, 1978). The degree of covalent binding of 1,1-DCE metabolites has been shown to be higher in kidney than in liver in both rats and mice (McKenna et al., 1977; Short et al., 1977a) and more water-soluble ^{14}C radioactivity has been found in fasted than fed rats (Jaeger et al., 1977a). Inhalation exposure of mice and rats to 60 ppm for 23 hr/day for up to 5 days produced renal lesions in mice but not in rats (Short et al., 1977b). The primary renal lesion observed after continuous exposure to 47 ppm for 90 days was nuclear hypertrophy of the tubular epithelium (Prendergast, et al., 1967).

3. CNS

Like other members of the chlorinated ethylene series, the DCEs possess general anesthetic or narcotic properties. However, there are virtually no data characterizing either short-term or long-term effects of DCEs on the CNS. It has been reported that the primary effect of acute inhalation of 1,1-DCE is CNS depression (Irish, 1963).

Inhalation exposures to trans-1,2-DCE, either 200 ppm for 8 hr/day, 5 days/week for 16 weeks or to 3000 ppm for one 8 hour exposure, failed to produce pre-narcotic signs or narcosis (Freundt _et_ _al_., 1977). The cis-isomer did not anesthetize rats in 4 hrs at 8000 ppm, but at 16,000 ppm they were anesthetized in 8 minutes and killed in 4 hours (Irish, 1963).

Two studies on the behavioral toxicity of 1,2-dichloroethylene have been published. Kallman, _et_ _al_.(1983) used taste aversion to saccharin in drinking water as an assay in male CD-1 mice. They reported that 1,2-dichloroethylene (given in an emulsified mixture of water and vegetable oil by intubation) produced a statistically significant ($P \leq 0.01$) saccharin aversion. The dose which reduced saccharin preference by 50% was 145 mg/kg (95% confidence limit= 80-230 mg/kg). De Ceaurriz, _et_ _al_. (1983) used an assay in which male Swiss OF1 mice (20-25 g) were exposed to levels of 1500-2000 ppm 1,2-dichloroethylene by inhalation for 4 hours and then forced to swim in a restricted area. The characteristic period of immobility induced by this treatment was decreased in a dose-dependent manner in the concentration range under consideration.

4. Heart

Inhalation of 1,1-DCE by rats at high concentrations (25,600 ppm) for 10 minutes has been found to sensitize the myocardium to both epinephrine-induced and non-epinephrine-induced arrhythmias. The cardiac sensitizing effects of 1,1-DCE were increased by phenobarbital pretreatment, suggesting that a metabolite of 1,1-DCE may be responsible for the cardiotoxicity (Siletchnik and Carlson, 1974). However, the metabolites are not known to sensitize the heart.

Inhalation of trans-1,2-DCE by rats at high concentrations (3,000 ppm) for 8 hr was reported to produce fibrous swelling of the cardiac muscle and hyperemia which persisted for 14 hr after exposure (Freundt et al., 1977).

5. Pancreas

As reported for a number of other chlorinated hydrocarbon solvents, 1,1-DCE increases bile duct pancreatic fluid flow in fasted rats. The composition of the fluid did not differ significantly from that in control animals (Hamada and Peterson, 1977). The significance of this finding remains to be established.

6. Immune System

Trans-1,2-DCE was screened for potential immunological effects in CD-1 mice (Munson, et al., 1982). Four-week old males were exposed for 14 consecutive days to the compound by gavage in a volume of 0.01 ml/g body weight at doses equal to 0.01 x LD_{50} (~ 22 mg/kg) and 0.1 x LD_{50} (~ 220 mg/kg). The LD_{50} for male mice was determined in range-finding studies to be 2221 (range=1987-2469) mg/kg. No changes in body weight or organ weight (liver, kidney, thymus, brain and lung) were observed over the test period.

The humoral immune response was assessed by measuring the number of IgM antibody-forming cells (AFC) to sheep RBCs. On the AFC/spleen basis, trans-1,2-DCE showed a trend towards producing immunosuppression ($P<0.1$).

Cell-mediated immune response was measured by quantifying the extravasation of human serum albumin during the delayed hypersensitivity response to sheep RBCs. Trans-1,2-dichloroethylene showed no effect at either dose.

7. Lung

Krijgsheld, et al. (1983) administered 1,1-dichloroethylene to male C57BL/6J mice (ip, 125 mg/kg, in olive oil) and after 24 hours found a decrease in cytochrome P-450 and other enzymes in the lung microsomes. They also reported that necrosis was restricted to the non-ciliated bronchiolar epithelial (Clara) cells. Forkert and Reynolds (1982) administered 1,1-dichloroethylene (100 mg/kg po in mineral oil) to mice of the same strain. The Clara cells showed extensive dilation of cisternae and degeneration of the endoplasmic reticulum. However, six hours after a 200 mg/kg dose both the Clara cells and the ciliated cells were necrotic and bronchiolar epithelial linings were exfoliated. After 24 hours, pulmonary edema, hemorrhage and focal atelectasis were present. Hypoxia also was noted at 24 hours. The lungs were, however, completely recovered seven days later. In addition, Forkert, et al. (1982) showed that dramatic changes in the subunit composition of pulmonary lactate dehydrogenase isozymes occurred following po administration of 100-

200 1,1-dichloroethylene/kg to the same mice (in mineral oil). (These changes in isozyme composition were not observed in kidney even though total lactate dehydrogenase activity was decreased in that tissue). Thus, pulmonary damage of 1,1-dichloroethylene can be demonstrated even when inhalation is not the route of administration.

C. Teratogenicity

The teratogenic potential of inhaled 1,1-DCE has been evaluated in rats and rabbits (Murray et al., 1979). Inhalation exposure for both species was for 7 hr/day at 20 (rats only), 80 or 160 ppm. Administration of 1,1-DCE to rats was on days 6 to 15 of gestation and on days 6 to 18 for rabbits. In rats, inhalation of 80 and 160 ppm of DCE produced significant maternal effects including decreased weight gain, decreased food consumption, increased water consumption and increased liver weight (160 ppm only). In the offspring, there was a significantly increased incidence of skeletal alterations at 80 and 160 ppm; these alterations included delayed ossification of various bones and wavy ribs. In rabbits, 160 ppm caused a significant increase in resorptions in the dams and a significant change in several minor skeletal variations in the offspring. In both rats and rabbits exposed to 1,1-DCE by inhalation, Murray et al.,(1979) noted that concentrations which caused little evidence of maternal toxicity (20 ppm in rats and 80 ppm in rabbits) caused no adverse effect on embryonal or fetal development.

The teratogenic potential of ingested 1,1-DCE also has been evaluated in rats (Murray et al., 1979). Drinking water containing 200 ppm 1,1-DCE, corresponding to an approximate dose of 40 mg/kg bw/

day, was administered on days 6 to 15 of gestation. The authors described this concentration as near the upper solubility limit of the compound in water. Data on maternal body weight gain, food and water consumption, and maternal liver weight showed no evidence for maternal toxicity. There was no significant effect on the average number of implantations, live fetuses or resorptions, and no alteration of the fetal sex ratio or body weight occurred. The only significant effect noted was an increase in mean fetal crown rump length. The authors concluded that 1,1-DCE was not teratogenic at this exposure level.

A study of the teratogenic potential of inhaled 1,1-DCE in rats and mice has been reported in an abstract (Short et al., 1976). Rats or mice were exposed for 23 hr/day from days 6 to 16 of gestation. The authors reported that no gross soft tissue or skeletal malformations attributable to exposure to 1,1-DCE were observed in rats exposed to up to 460 ppm or in mice exposed to 15 ppm.

D. Mutagenicity

1,1-DCE has been shown to be mutagenic in *Salmonella typhimurium* strains TA 1530, TA 100 (Bartsch *et al.*, 1975; Simmon *et al.*, 1977; Simmon and Tardiff, 1978) and TA 1535 (Jones and Hathway, 1978c) and in *E. coli* K12 (Greim *et al.*, 1975). In both bacterial systems, mutagenic activity required microsomal activation. Microsomal fractions derived from liver, kidney and lung of mice and rats were used to determine their relative ability to convert 1,1-DCE into mutagenic metabolites (Bartsch *et al.*, 1975). Data comparing the relative activity of these various tissues are in Table

V-3. Mouse liver, kidney and lung fractions were all effective, with liver showing the greatest activity. A much lower mutagenic response was observed in rats than in mice with liver and kidney fractions and there was only minimal activity with the lung fraction in either species. Human liver also was found to convert 1,1-DCE into mutagenic metabolites, its activity being similar to rat liver and considerably less than mouse liver (Bartsch, 1976).

Pretreatment of rats with modifiers of microsomal enzymes affected the bacterial mutagenicity of 1,1-DCE in the presence of S-9 from liver from these animals (Table V-3). In general, microsomal enzyme inducers increased and inhibitors of microsomal P-450 decreased the mutagenicity of 1,1-DCE. Microsomal fractions derived from kidney and lung from animals pretreated with phenobarbital also increased the mutagenicity of 1,1-DCE (Bartsch _et_ _al_., 1975).

Both cis- and trans-1,2-DCE were non-mutagenic when assayed with _E_. _coli_ K12 at similar concentrations used for 1,1-DCE (Greim _et_ _al_., 1975). It has been proposed that the mutagenic and presumably carcinogenic activities of chloroethylenes are related to the symmetry of the chlorine substitution of the epoxide intermediates formed by oxidation of the parent olefins. Compounds with unsymmetrical chlorine substitution would result in less stable, more reactive intermediates than symmetrically substituted materials (Henschler _et_ _al_., 1976; Henschler, 1977; Henschler and Bonse, 1977). These data support this hypothesis, at least with respect to mutagenesis in _E_. _coli_ K12 systems. However, generalization of this hypothesis to carcinogenesis in intact animals is not possible.

Table V-3

Effect of Different Tissues on the *In Vitro* Bacterial Mutagenicity of 1,1-DCE

Species	Organ	Relative Activity
Mouse	Liver	100
	Kidney	20
	Lung	6
Rat	Liver	30
	Kidney	5
	Lung	3
Human[a]	Liver	20[b]

a Biopsy samples

b Tissue samples were from 4 patients: relative activity for the individual patients was 11, 16, 17, 38.

Based on Bartsch, 1976; Bartsch *et al*., 1976; Bartsch *et al*., 1979.

Table V-4

Effect of Drug Treatment of Rats on Liver S-9 Mediated Bacterial Mutagenicity of 1,1-DCE

Drug Treatment	Relative Activity
None	100
Phenobarbital	200
Pregnenolone-16-α-carbonitrile	60
3-Methylcholanthrene	150
Aminoacetonitrile	40
Dibenamine	70
Disulfiram	10
Disulfiram (added *in vitro*)	10

Based on Bartsch *et al*., 1979.

1,1-DCE was tested for its ability to induce both point mutation and mitotic gene conversion in the yeast *Saccharomyces cerevisiae* D7 in a suspension test with and without metabolic activation and in the intrasanguineous host-mediated assay in mice (Bronzetti, *et al*., 1981). The chemical was tested at levels of 0, 10, 20, 30, 40 or 50 mM/plate, with a 2-hour exposure period. Without metabolic activation, 1,1-DCE was toxic at all levels, but not genetically active. When mouse liver 10,000g activation system was added, concentration-dependent increases in both mutant and convertant frequencies were seen at concentrations above 20 mM.

When 1,1-DCE was administered to mice by gavage at 400 mg/kg in the intrasanguineous host-mediated assay, the induction of gene conversion at the trp 5 locus was detected in liver and kidney; no significant increase was seen in the lungs. The same dose also induced ilv-92 reversion in the kidney and liver, but not the lung.

After multiple treatments with 1,1-DCE by gavage (100 mg/kg in 0.5 ml corn oil 5 days/week for 23 administrations followed by 200 mg/kg on the day of the assay;total dose=2500 mg/kg), increased frequency of trp 5 conversions and ilv-92 reversions were seen in the liver and kidney, but not the lungs.

Both 1,1-DCE and cis-1,2-DCE were found to be mutagenic in the host-mediated assay using *Salmonella* tester strains in mice, whereas trans-1-2-DCE was found to be non-mutagenic (Cerna and Kypenova, 1977). Of the three isomeric DCEs, only cis-1,2-DCE produced chromosomal aberrations in cytogenetic analysis of bone marrow cells following repeated intraperitoneal injections (Cerna and Kypenova, 1977).

1,1-DCE was found to be non-mutagenic in V79 Chinese hamster cells in the presence of 15,000 g liver supernatant from phenobarbital-pretreated rats and mice (Drevon and Kuroki, 1979).

The finding of increased mutation rates in bacterial systems has not been confirmed in mammalian systems. CD-1 male mice exposed to 10, 30, or 50 ppm of 1,1-DCE for 6 hr/day for 5 days failed to produce dominant lethal mutations (Anderson, 1977). In this study there was a pre-implantation loss as reflected by an increase in the number of females that did not become pregnant after mating with exposed males (at the 50 ppm level only). However, there was no pre-implantation loss in those females that did become pregnant. In addition, post-implantation loss is more indicative of dominant lethality than is a pre-implantation loss. Similarly, adult CD male rats exposed to 55 ppm 1,1-DCE for 6 hr/day, 5 days/week for 11 weeks failed to produce dominant lethal mutations (Short, et al., 1977c).

E. Carcinogenicity

The carcinogenicity of 1,1-dichloroethylene has been evaluated in gavage studies with rats and mice sponsored by the National Toxicology Program (NTP, 1982). The following discussion is, in large part, taken directly from the NTP Bioassay report.

A single-dose range-finding study was conducted to determine the doses for the 14-day repeated dose study. 1,1-DCE was diluted in corn oil and administered by gavage to groups of five males and five females/species in doses of 0, 10, 50, 100, 500 or 1000 mg/kg. The animals were observed for 14 days and necropsied on Day 15.

One female rat receiving 500 mg/kg died. One male rat that received 10 mg/kg died after 7 days and two that received 1000 mg/kg died within 48 hours.

All male mice receiving 500 or 1000 mg/kg died. Among the female mice, 1/5 receiving 50 mg/kg, 3/5 receiving 500 mg/kg and 5/5 receiving 1000 mg/kg died.

Fourteen-day repeated dose studies were conducted to determine the doses to be used in the 90-day subchronic studies. Groups of five males and five females/species were administered 1,1-DCE in corn oil by gavage, daily for 14 days. On Day 16, all survivors were sacrificed and necropsied. Doses administered, survival and mean body weights of the dosed and control groups are shown in Tables V-5 and V-6.

Four of five male rats receiving 1000 mg/kg, 3/5 female rats receiving 500 mg/kg and 3/5 females receiving 1000 mg/kg died within 48 hours. All were hyporeactive. Weight gain of male rats receiving 500 mg/kg was depressed 28%; the only surviving male rats receiving 1000 mg/kg lost weight. A dose-related decrease in mean body weight gain was observed in female rats. Weight gain was depressed 62% and 129% in females receiving 500 or 1000 mg/kg, respectively.

All mice receiving 500 mg/kg died. Before death, they exhibited hyporeactivity, a staggering gait and rapid breathing. Hemorrhagic necrosis of the liver was seen at necropsy. No compound-related histopathology was observed in the mice.

90-Day subchronic studies were performed to determine the doses to be used in the chronic studies. Groups of 10 rats and 10 mice of each sex were administered 1,1-DCE in corn oil by gavage 5 times/week at 0, 5, 15, 40, 100 or 250 mg/kg for 13 weeks. Vehicle control groups consisting of 10 males and 10 females of each species received corn oil alone. After 90 days, survivors

TABLE V-5

DOSAGE, SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED 1,1-DCE BY GAVAGE FOR 14 DAYS

(NTP, 1982)

Dose (mg/kg)	Survival(a)	Mean Body Weights (grams) Initial	Final	Change (b)	Weight Change Relative to Controls (%)(c)
Male					
0	5/5	116.8 ± 6.57	163.4 ± 6.79	46.6 ± 7.77	----
10	5/5	110.6 ± 4.83	165.4 ± 9.24	54.8 ± 4.72	+ 17.6
50	5/5	112.0 ± 1.79	158.2 ± 4.39	46.2 ± 3.25	- 0.9
100	5/5	109.0 ± 4.68	151.8 ± 9.58	42.6 ± 9.11	- 8.6
500	5/5	114.0 ± 5.08	147.4 ± 2.25	33.4 ± 5.36	- 28.3
1000	5/5	118.0 ± 0.00	114.0 ± 0.00	-4.0 ± 0.00	-108.6
Female					
0	5/5	94.6 ± 4.46	120.6 ± 8.62	26.0 ± 5.06	----
10	5/5	97.2 ± 3.47	126.2 ± 1.56	29.0 ± 2.39	+ 11.5
50	5/5	97.0 ± 3.16	121.6 ± 1.56	24.6 ± 4.02	- 5.4
100	5/5	97.4 ± 2.48	120.4 ± 3.14	23.0 ± 1.79	- 11.5
500	5/5	102.0 ± 6.00	112.0 ±11.00	10.0 ± 5.00	- 61.5
1000	5/5	100.5 ± 0.50	93.0 ± 7.00	-7.5 ± 6.50	- 128.8

(a) Number surviving/number at start. All calculations are based on numbers surviving to end of study

(b) Mean weight change of the survivors of the group ± standard error of the mean.

(c) Weight change of dosed survivors relative to survivors of the controls=

$$\frac{\text{Weight change (Dosed group) - Weight change (Control group) x 100}}{\text{Weight change (Control group)}}$$

TABLE V-6

DOSAGE, SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED 1,1-DCE BY GAVAGE FOR 14 DAYS

(NTP, 1982)

Dose (mg/kg)	Survival(a)	Mean Body Weights (grams)			Weight Change Relative to Controls (%)(
		Initial	Final	Change (b)	
Male					
0	5/5	22.2 ± 0.37	24.8 ± 0.37	2.6 ± 0.40	——
5	5/5	22.0 ± 0.32	23.4 ± 0.40	1.4 ± 0.40	- 46.2
10	5/5	23.0 ± 0.84	25.8 ± 0.86	2.8 ± 0.66	+ 7.7
50	5/5	22.2 ± 0.80	24.8 ± 0.97	2.6 ± 0.51	0.0
100	5/5	22.8 ± 0.37	24.0 ± 0.32	1.2 ± 0.20	- 53.8
500	0/5	(d)	(d)	(d)	
Female					
0	5/5	20.2 ± 0.20	21.6 ± 0.40	1.4 ± 0.40	——
5	5/5	20.6 ± 0.40	21.2 ± 0.20	0.6 ± 0.40	- 57.1
10	5/5	20.4 ± 0.40	21.0 ± 0.63	0.6 ± 0.60	- 57.1
50	5/5	20.4 ± 0.24	21.0 ± 0.32	0.6 ± 0.24	- 57.1
100	5/5	21.0 ± 0.32	22.2 ± 0.49	1.2 ± 0.73	- 14.3
500	0/5	(d)	(d)	(d)	

(a) Number surviving/number at start. All calculations are based on numbers surviving to of study

(b) Mean weight change of the survivors of the group ± standard error of the mean.

(c) Weight change of dosed survivors relative to survivors of the controls=

$$\frac{\text{Weight change (Dosed group) - Weight change (Control group) x 100}}{\text{Weight change (Control group)}}$$

(d) No data are presented due to 100% mortality in this group were sacrificed and necropsied.

Representative tissues from rats and mice receiving 250 mg/kg, from mice receiving 100 mg/kg and from control animals were examined microscopically. Livers from all other dose groups also were examined. The doses administered, survival and the mean body weights at Week 13 are shown in Tables V-7 and V-8.

Three female rats receiving 250 mg/kg died during the first week. No other rats died. Weight gain was depressed 20% for male rats receiving 250 mg/kg compared with controls.

Severe centrilobular necrosis of the liver was observed in the 3 female rats that died (Table V-9). Minimal to moderate hepatocytomegaly was seen in the rest of the rats that received 250 mg/kg. Lesser degrees (minimal to mild) of hepatocytomegaly were seen in 6/10 male rats and 3/10 female rats that received 100 mg/kg. Various combinations of portal and subcapsular fibrosis, bile duct hyperplasia, pigmented macrophages and hepatocellular atrophy were seen in all male rats (mild to severe in 9/10 and minimal in the other) and in 7/10 female rats (mild to moderate in 6/10 and minimal in 1/10) receiving 250 mg/kg. The rats receiving 100 mg/kg were affected to a much lesser degree, both in numbers and in severity. Foci of cytoplasmic changes, primarily clear cell foci, were seen in 3/10 males and 3/10 females receiving 250 mg/kg. Fatty metamorphosis or cytoplasmic vacuolization or both, usually in minimal or mild degrees of severity, occurred in the animals of most groups but had no distinct dose relationship.

Original examination of the lesions in the rat livers placed more emphasis on the changes seen in the animals at the lower

TABLE V-7

DOSAGE, SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED 1,1-DCE BY GAVAGE FOR 13 WEEKS

(NTP, 1982)

Dose (mg/kg)	Survival(a)	Mean Body Weights (grams) Initial	Final	Change	Weight Change Relative to Controls (%)(b)
Male					
0	10/10	118	316	+198	——
5	10/10	115	307	+192	- 3
15	10/10	115	306	+191	- 4
40	10/10	119	302	+183	- 8
100	10/10	117	299	+182	- 8
250	10/10	117	276	+159	-20
Female					
0	10/10	95	200	+105	----
5	10/10	93	193	+100	- 5
15	10/10	93	198	+105	0
40	10/10	97	194	+ 97	- 8
100	10/10	95	194	+ 99	- 6
250	7/10	97	190	+ 93	-11

(a) Number surviving/number at start. All calculations are based on numbers surviving to end of study

(b) Weight change of dosed survivors relative to survivors of the controls=

$$\frac{\text{Weight change (Dosed group) - Weight change (Control group) x 100}}{\text{Weight change (Control group)}}$$

TABLE V-8

DOSAGE, SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED 1,1-DCE BY GAVAGE FOR 13 WEEKS

(NTP, 1982)

Dose (mg/kg)	Survival(a)	Mean Body Weights (grams)			Weight Change Relative to Controls (%)(b)
		Initial	Final	Change	
Male					
0	10/10	21	35	+14	—
5	10/10	21	35	+14	0
15	10/10	21	34	+13	- 7
40	9/10	21	33	+12	-14
100	8/10	21	30	+ 9	-36
250	0/10	21	—	—	—
Female					
0	10/10	18	24	+ 6	—
5	9/10	19	23	+ 4	-33
15	9/10	18	23	+ 5	-17
40	10/10	18	23	+ 5	-17
100	7/10	18	23	+ 5	-17
250	1/10	20	26	+ 6	0

(a) Number surviving/number at start. All calculations are based on numbers surviving to en of study

(b) Weight change of dosed survivors relative to survivors of the controls=

$$\frac{\text{Weight change (Dosed group) - Weight change (Control group)} \times 100}{\text{Weight change (Control group)}}$$

Table V-9

Incidence of Liver Lesions in Rats and Mice Administered 1,1-DCE by Gavage for 13 Weeks

(NTP, 1982)

Dose (mg/kg)	Controls		5		15		40		100		250	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Rats												
No. examined	9	10	10	10	10	10	10	10	10	10	10	10
Centrilobular necrosis	0	0	0	0	0	0	0	0	0	0	0	0
Fibrosis, pigmentation, bile duct hyperplasia, hepatocellular atrophy	0	0	0	0	0	0	0	0	3	4	10	7
Fatty metamorphosis	4	0	7	5	7	7	8	3	2	2	0	1
Hepatocytomegaly	0	0	0	0	0	0	1	0	6	3	10	7
Foci of cytoplasmic change	0	0	0	0	0	0	0	0	0	0	3	3
Mice												
No. examined	10	10	10	10	10	10	10	10	10	10	10	10
Cellular necrosis	0	0	0	0	0	0	0	0	2	2	5	5
Congestion	0	0	0	0	0	0	2	0	0	0	8	2
Necrosis, NOS	0	0	0	0	0	0	0	0	0	0	2	0
Cellular atypia	0	0	0	0	0	0	2	0	7	6	0	0
Fatty metamorphosis	0	0	0	1	2	0	2	2	0	0	0	0
Focal area of cellular	0	0	1	0	0	0	0	0	0	0	0	0

doses whereas a review interpreted these changes to be less important. Thus, the doses of 1 and 5 mg/kg, which were selected for the chronic study and were originally based upon hepatotoxic effects, were probably too low.

All male mice receiving 250 mg/kg died within 24 hours; 9/10 females receiving 250 mg/kg died within 48 hours. Deaths occurred in 1/10 females receiving 5 mg/kg; 1/10 females receiving 15 mg/kg; 1/10 males receiving 40 mg/kg; and 2/10 males and 3/10 females receiving 100 mg/kg. A dose-related decrease in body weight gain was observed for male mice.

Centrilobular necrosis, hemorrhage and congestion of the liver were observed in males and females that died in the 250 mg/kg group (Table V-9). Cellular atypia of the liver (less severe than that seen in the rats) was observed in 7/10 males and 6/10 females receiving 100 mg/kg but not in animals receiving 250 mg/kg. At 40, 15 and 5 mg/kg, severity of hepatic lesions was dose-related. The incidence of hepatic lesions in males was dose-related and higher than in the females. The most frequently encountered change in mice exposed at 40 mg/kg or less was slight, sometimes moderate, fatty metamorphosis. Patchy foci of one or a few smaller cells with sparse cytoplasm were encountered much less frequently in mice than in rats.

Hepatic effects were considered to be minimal at 5 mg/kg and doses selected for the mice for the chronic study were 2 and 10 mg/kg.

In the chronic study, rats and mice were grouped 50 sex/group with controls receiving corn oil alone. Rats were dosed at 1 or 5 mg/kg, mice at 2 or 10 mg/kg. Doses were administered 5 times per week by gavage for 104 weeks.

The animals were examined twice daily for morbidity and mortality and weighed every two weeks. At necropsy, gross and microscopic examinations were performed on major tissues, major organs and all gross lesions from sacrificed animals and those found dead.

Mean body weights of dosed and control rats of either sex were comparable throughout the study. No compound-related clinical signs were observed.

While no significant differences in probability of survival were observed in any group, 12 control and 10 low-dose males died as a result of a 5-hour temperature excursion during week 82 of the study and 1 low-dose male was accidentally killed during week 42. These animals were censored in the survival analysis but were examined histologically.

In male rats, 20/50 (40%) of the vehicle controls, 24/50(48%) of the low dose and 37/50(74%) of the high dose group survived to the end of the study. In the females, 27/50(54%) of the vehicle controls, 28/50(56%) of the low dose and 29/50 (58%) of the high dose group lived to the end of the study.

The number of accidental deaths may have influenced the incidence of late appearing tumors in the control and low dose males. The tumors found were common to aging rats, occurring at comparable rates in control and treated animals. None were considered to be treatment-related.

Several non-neoplastic lesions of possible significance were observed. The incidence of chronic inflammation of the kidney in both male and female rats was higher in the high dose groups than in the controls (males:controls=26/50,52%; low dose=24/48,50%; high dose= 43/48,90%; females: controls= 3/49,6%; low dose= 6/49,12%; high dose= 9/44, 20%). Although the occurrence of chronic nephritis appears to be dose-related, this lesion is common in aging rats.

All of the increased tumor incidences that were statistically significant by the Fisher exact test or by the Cochran-Armitage linear trend test were not significant when life table analyses were used. This difference occurs when life table analyses adjust for intercurrent mortality and thus they minimize the impact of animals dying before the onset of late-appearing tumors. This adjustment was particularly critical for the analyses of tumor incidence in male rats because of the accidental deaths among the male rats.

Among the mice, the mean body weights of dosed male mice were lower than those in the control group. Mean body weights of high dose and control females were comparable. Mean body weights of low dose mice of either sex were lower than those of high dose or vehicle control mice. No compound-related clinical signs were observed.

No significant differences in survival were observed between any groups of male mice. A significant reduction in the survival of female mice was observed in the low dose group when compared with the high dose group.

In male mice, 33/50 (66%) of the vehicle controls, 35/50 (70%) of the low dose and 36/50 (72%) of the high dose group survived to the end of the study. In female mice, 40/50 (80%) of the vehicle controls, 32/50 (64%) of the low dose and 42/50 (84%) of the high dose groups lived to the end of the study.

Non-neoplastic lesions including necrosis of the liver (focal, multifocal and diffuse) were observed more frequently in dosed mice than in controls (males: controls= 1/46,2%; low dose= 3/46,7% and high dose= 7/49,14%; females: controls= 0/47,0%; low dose= 4/49,8% and high dose= 1/49, 2%). The incidence of lung inflammation was slightly below that normally seen in 2-year old B6C3F1 mice.

Neoplastic lesions observed in dosed mice were considered to be unrelated to the administration of 1,1-DCE. The only observed significant ($P<0.05$) increase in tumor incidence occurred in low dose female mice: lymphoma (2/48,9/49,6/50) and lymphoma or leukemia (7/48,15/49,7/50). These increases were not considered to be related to the administration of 1,1-DCE because similar effects were not found in the high dose female mice or male mice or rats of either sex.

It was concluded by NTP that, under the conditions of this bioassay, 1,1-DCE administered by gavage was not carcinogenic for F344 rats or B6C3F1 mice of either sex. NTP went on to say, however, that since the use of the maximum tolerated dose in this study has not been clearly demonstrated and since previously reported studies have shown that carcinogenicity is associated with inhalation exposure to 1,1-DCE, this study should not be taken as proof that the chemical is not a carcinogen.

Additional studies of the potential carcinogenicity of 1,1-DCE have been conducted with mice, rats and hamsters using either oral administration or inhalation exposure. Preliminary results after a total of 98 weeks' observation have been reported (Maltoni, 1977; Maltoni et al., 1977). In the inhalation study, Swiss mice were exposed to 10 or 25 ppm of 1,1-DCE for 4 hours/day, 4 or 5 days/week for 52 weeks and then observed for the remainder of the study. Data from this study are in Tables V-10 and V-11. Exposure to 10 ppm of 1,1-DCE caused no statistically significant increase in the incidence of any tumor. At 25 ppm, 17 of the mice exposed to 1,1-DCE had developed kidney adenocarcinomas compared to none in the control group (Table V-10). The majority of the tumors were observed in male mice. In contrast, no kidney adenocarcinomas were observed in Sprague-Dawley rats under the same exposure regimen at exposures up to 200 ppm. Data from this study also showed a significant increase in mammary adenocarcinoma in Swiss mice inhaling 25 ppm (Table V-11) and in Sprague-Dawley rats inhaling 100 or 150 ppm of 1,1-DCE (Table V-12) (Maltoni et al., 1977). At 10, 25 or 50 ppm of 1,1-DCE, there was no increase in tumor incidences in Sprague-Dawley rats. Oral administration of 20 mg/kg of 1,1-DCE 4 to 5 days/week for 52 weeks to female Sprague-Dawley rats resulted in a 42% incidence of mammary tumors, whereas control animals had a 34% incidence. This is not a statistically significant difference. Hamsters exposed by inhalation to 25 ppm of 1,1-DCE did not exhibit an increased tumor incidence (Maltoni, 1977; Maltoni et al., 1977). Additionally, it has been reported indirectly that other studies by Maltoni found no statistically significant increased incidence

Table V-10

Kidney Adenocarcinomas in Swiss Mice Exposed to 1,1-DCE via Inhalation [a]

1,1-DCE, ppm	Sex	Total Animals at Risk[b]	No. Animals With Adenocarcinoma	%
0	Male[c]	54	0	0
0	Female[c]	49	0	0
0	Male[d]	46	0	0
0	Female[d]	52	0	0
10	Male[d]	22	0	0
10	Female[d]	20	0	0
25	Male[c]	78	16	20.5
25	Female[c]	65	1	1.5

[a] 4 hr/day, 4-5 days/week for 12 months

[b] Defined here as the number of animals that had died since the appearance of the first tumor; or (survivors at the time of the first tumor) - (survivors at the time these preliminary data were reported).

[c] Animals were 9 weeks of age at start of exposure.

[d] Animals were 16 weeks of age at start of exposure.

Based on Maltoni *et al.*, 1977

Table V-11

Incidence of Mammary Adenocarcinomas in Female Swiss Mice Receiving 1,1-DCE via Inhalation[a]

	1,1-DCE Concentration, ppm			
	0	10	0	25
Age at start of test (weeks)	16	16	9	9
Number with tumors/ number at risk[b]	2/52	1/20	0/49	7/65
Incidence (%)	3.8	5.0	0	10.8
p-values[c]	—	0.63	—	0.017

[a] 4 hr/day, 4-5 days/week for 12 months

[b] Number at risk defined here as the number of animals that had died since the appearance of the first tumor (a kidney adenocarcinoma); or (survivors at time of the first tumor) - (survivors at the time these preliminary data were reported).

[c] Calculated using Fisher exact test and matched control incidence.

Based on Maltoni _et_ _al_., 1977.

Table V-12

Incidence of Mammary Tumors in Sprague-Dawley Rats Inhaling 1,1-DCE

	1,1-DCE Concentration, ppm					
	0	10	25	50	100	150
Number with tumors / Number initially	32/100	15/30	12/30	15/30	18/30	35/60
Incidence (%)	32	50	40	50	60	58
p-values[b]	------	0.058	0.27	0.058	0.0058	0.001

[a] 4 hr/day, 4-5 days/week for 12 months

[b] Calculated using the Fisher exact test.

Based on Maltoni *et al*., 1977.

of any tumor in BALB/C, C56BL, or C_3H mice (Fishbein, 1979).

In another inhalation study (Lee et al., 1978), CD-1 mice and CD rats were exposed to 55 ppm of 1,1-DCE for 6 hr/day, 5 days/week for 7 to 12 months. Hepatic hemangiosarcomas were observed in the mice exposed to 1,1-DCE: 2/35 for males and 1/35 for females in the treated group compared to 0/26 for males and 0/36 for females in the control group. The significance of these hepatomas was was judged to be questionable because such tumors have been reported to occur spontaneously. However, two rats developed hemangiosarcomas in the mesenteric lymph node or subcutaneous tissue which were judged probably to be caused by 1,1-DCE. Although kidney pathology was observed, there was no report of adenocarcinoma.

An inhalation study using both Wistar rats and Sprague-Dawley rats has been reported (Viola and Caputo, 1977). Exposures were to 1,1-DCE concentrations from 75 to 200 ppm for 4 hr/day, 5 days/week for 12 months. Data from this study, summarized in Table V-13, were interpreted as showing no grossly observable correlation between tumor production and 1,1-DCE inhalation.

Additionally, male and female Sprague-Dawley rats were exposed to 1,1-DCE by inhalation (25 or 75 ppm for 6 hr/day, 5 days/week for 18 months). In the interim report of this study (Rampy et al., 1977), there was no evidence of increased tumor incidence in animals treated with 1,1-DCE. The data are summarized in Table V-14. The only adverse effects found were minimal microscopic changes in the liver with a higher incidence at 75 ppm than at 25 ppm. In all other respects there were no observed differences between control and treated groups.

Table V-13

Incidence of Tumors in Rats Inhaling 1,1-DCE[a]

1,1-DCE, ppm	Sex	Number of Rats	Number of Tumor-Bearing Animals	% of Total	Types of Tumors
Wistar Rats					
0	M	30	5	17	Abdominal cavity (5)
0	F	30	10	33	Abdominal cavity (9) Lung (1)
b	M	51	8	16	Abdominal cavity (7) Liver (1)
b	F	23	9	39	Abdominal cavity (8) Lung (1)
Sprague-Dawley Rats					
0	M	30	0	0	
0	F	30	15	50	Subcutaneous fibromas (15)
75	M	16	1	6	Subcutaneous fibromas (1)
75	F	21	9	43	Subcutaneous fibromas (9)
100	M	30	3	10	Abdominal lymphomas (3)
100	F	30	17	57	Subcutaneous fibromas (16) Abdominal lymphoma (1)

---

[a] 4 hr/day, 5 days/week for 12 months.

[b] Exposure to 200 ppm for first 5 months, then reduced to 100 ppm.

Based on Viola and Caputo, 1977.

Table V-14

Grossly Observed Tumors in Sprague-Dawley Rats Inhaling 1,1-DCE[a]

Sex	Tumors	Exposure Level (ppm)	No. animals with tumor[b]	No. animals in group	Tumors, %
M	Subcutaneous tumor (mammary or midcervical region)	Control	8/6	86	7.0
		75	9/8	85	9.4
		25	8/7	86	8.1
M	Subcutaneous tumor (eye, ear or head region)	Control	2	86	2.3
		75	2	85	2.4
		25	5	86	5.8
M	Subcutaneous tumor (body or limb region)	Control	1	86	1.2
		75	4	85	4.7
		25	3	86	3.5
M	Liver nodule (tumor or mass)	Control	1	86	1.2
		75	2	85	2.4
		25	0	86	0
M	Kidney (primary site)	Control	3	86	3.5
		75	0	85	0
		25	0	86	0
F	Subcutaneous tumor (mammary or midcervical region)	Control	138/68	86	79.1
		75	159/74	84	88.1
		25	149/73	88	82.9
F	Subcutaneous tumor (eye, ear or head region)	Control	1	86	1.2
		75	1	84	1.2
		25	0	88	0
F	Subcutaneous tumor (body, limb region)	Control	2	86	2.3
		75	1	84	1.2
		25	2	88	2.3
F	Liver nodule (tumor or mass)	Control	2	86	2.3
		75	1	84	1.2
		25	0	88	0
F	Kidney (primary site)	Control	1	86	1.2
		75	1	84	1.2
		25	1	88	1.1

[a] 6 hr/day, 5 days/week for 18 months.

[b] Where two numbers appear, data represent number of tumors over number of animals with tumors. Percentage is based on number of animals with tumors.

Based on Rampy *et al*., 1977.

The effect of weekly oral administration of 50 mg/kg of 1,1-DCE following _in utero_ exposure (150 mg/kg on day 17 of gestation) was studied in BDIV rats (Ponomarkov and Tomatis, 1980). The oral administration was continued throughout the lifetime of the animals until the study was terminated after 120 weeks. The data are summarized in Table V-15. There was no statistically significant increase in the total number of tumor bearing animals. However, an increased incidence of tumors at certain sites was observed: liver tumors in females and meningiomas in males. Additionally, hyperplastic nodules of the liver were observed in both male and female rats; these were not seen in control animals. The authors concluded that the results provided limited evidence of carcinogenicity of 1,1-DCE.

Male and female Sprague-Dawley rats were exposed to 1,1-DCE in drinking water at 60, 100 or 200 ppm for two years, corresponding to average daily doses of 7, 10 or 20 mg/kg/day for males and 9, 14 or 30 mg/kg/day for females (Rampy, _et_ _al_.,1977; Quast, _et_ _al_., 1983). Details of the protocol are described in Section A of this chapter. Data from the interim report of this study (Rampy _et_ _al_., 1977), summarized in Table V-16, showed no evidence of increased tumor incidence in animals treated with 1,1-DCE. No adverse effect was observed in any of the treated groups compared to controls with two exceptions. The 60 ppm female group had a statistically higher incidence of pituitary gland adenomas than control animals. However, this was considered not to be an effect of the treatment, since it was not dose-related and Sprague-Dawley rats have a high and variable spontaneous

Table V-15

Tumor Incidence in BDIV Rats Treated Weekly with 1,1-DCE

	Dose of 1,1-DCE, mg/kg			
	0		50	
	Male	Female	Male	Female
Effective number of rats[a]	49	47	81	80
Tumor-bearing rats				
Number	16	24	31	53
%	32.7	51.1	38.3	66.3
Number of tumors				
Total	16	29	35	64
Per Rat	0.3	0.6	0.4	0.8
Animals with more than one tumor				
Number	0	5	4	11
%	0	10.6	4.9	13.8
Distribution of tumors				
Meninges				
Number	1	0	6	0
%	2.0	0	7.4	0
Oral cavity				
Number	2	1	5	1
%	4.1	2.1	6.2	1.3
Stomach				
Number	0	1	1	2
%	0	2.1	1.2	2.5
Liver				
Number	0	0	1	3
%	0	0	1.2	3.8
Soft tissue				
Number	4	0	9	7
%	8.2	0	11.1	8.8
Mammary gland				
Number	0	22	1	39
%	0	46.8	1.2	48.8
Ovary				
Number	0	3	0	6
%	0	6.4	0	7.5
Other				
Number	9	2	12	6
%	18.4	4.3	14.8	7.5
Liver hyperplastic nodules				
Number	0	0	2	6
%	0	0	2.5	7.5

The percentage and the number of tumors are expressed in relation to the effective number of rats.

[a] Survivors at the time the first tumors were observed.

Based on Ponomarkov and Tomatis, 1980.

Table V-16

Grossly Observed Tumors in Sprague-Dawley Rats Given 1,1-DCE in Drinking Water

Sex	Tumors	Dose (ppm)	No. animals with tumor[a]	No. animals in group	Tumors, %
M	Subcutaneous tumor (mammary or midcervical region)	Control	6/6	80	7.5
		200	6/4	47	8.5
		100	6/6	48	12.5
		60	6/6	48	12.5
M	Subcutaneous tumor (eye, ear or head region)	Control	4	80	5.0
		200	2	47	4.3
		100	0	48	0
		60	1	48	2.1
M	Subcutaneous tumor (body or limb region)	Control	2	80	2.5
		200	0	47	0
		100	0	48	0
		60	2	48	4.2
M	Nodular proliferation in liver (primary site)	Control	5	80	6.3
		200	0	47	0
		100	1	48	2.1
		60	1	48	2.1
M	Liver (metastatic foci)	Control	0	80	0
		200	0	47	0
		100	0	48	0
		60	1	48	2.1
M	Liver (diffuse tumor infiltrate and enlarged, associated with lymphoid)	Control	0	80	0
		200	0	47	0
		100	1	48	2.1
		60	2	48	4.2
M	Kidney (primary site)	Control	2	80	2.5
		200	0	47	0
		100	0	48	0
		60	1	48	2.1
F	Subcutaneous tumor (mammary and midcervical region)	Control	104/59	80	73.7
		200	64/36	48	75.0
		100	68/27	48	77.1
		60	71/40	48	83.3
F	Subcutaneous tumor (eye, ear and head region)	Control	1	80	1.3
		200	1	48	2.1
		100	2	48	4.2
		60	1	48	2.1

continued-

Table V-16 - continued

Sex	Tumors	Dose (ppm)	No. animals with tumor[a]	No. animals in group	Tumors, %
F	Subcutaneous tumor (body or limb region)	Control	0	80	0
		200	0	48	0
		100	1	48	2.1
		60	0	48	0
F	Nodular proliferation in liver (primary site)	Control	2	80	2.5
		200	3	48	6.3
		100	0	48	0
		60	2	48	4.2
F	Liver (metastatic foci)	Control	1	80	1.3
		200	0	48	0
		100	0	48	0
		60	0	48	0
F	Liver (diffuse tumor infiltrate and enlarged, associated with lymphoid)	Control	2	80	2.5
		200	0	48	0
		100	0	48	0
		60	0	48	0
F	Kidney (primary site)	Control	1	80	1.3
		200	0	48	0
		100	1	48	2.1
		60	0	48	0

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[a] Where two numbers appear, data represent number of tumors over number of animals with tumors. Percentage is based on number of animals with tumors.

Based on Rampy *et al.*, 1977.

incidence of this tumor. The other effect was a dose-related, statistically significant incidence of liver lesions, described as fatty degeneration which was more marked in females than in males. Accompanying this was atrophy of the centrilobular cells and hypertrophy of the periportal liver cells. Treatment-related necrosis of cells was not observed.

The carcinogenic effects of 1,1-DCE also were investigated in Ha:ICR Swiss mice by several routes of administration (Van Duuren et al., 1979). 1,1-DCE was inactive as a whole mouse skin carcinogen and inactive by subcutaneous injection. In the two stage carcinogenesis assay using phorbal myristate acetate (PMA) as a promoter, 1,1DCE administered as a single dose of 121 mg was shown to be active as a skin tumor initiator. These data are not sufficient to suggest that 1,1-DCE should be regulated as a carcinogen since it is unlikely that environmental exposure would occur to the substance and a phorbol ester such as PMA.

Table V-17 contains a summary of the results of the several carcinogenicity studies described in detail above.

There are no reported data to show if cis-1,2-DCE or trans-1,2-DCE is or is not a chemical carcinogen.

Table V-17

Summary of Results from Carcinogenicity Studies with 1,1-DCE

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Swiss Mice	10 ppm	98 weeks	negative	Maltoni, 1977; Maltoni *et al.*, 1977
		25 ppm for 12 months	98 weeks	positive	
Inhalation	CD-1 Mice	55 ppm	52 weeks	negative	Lee *et al.*, 1978
Not Reported	BALB/C Mice	Not Reported	Not Reported	negative	Fishbein, 1979 Report of Maltoni studies
	C56 BL Mice	Not Reported	Not Reported	negative	
	C_3H Mice	Not Reported	Not Reported	negative	
Inhalation	Sprague-Dawley Rats	10 ppm	98 weeks	negative	Maltoni, 1977; Maltoni *et al.*, 1977
		25 ppm	98 weeks	negative	
		50 ppm	98 weeks	negative	
		100 ppm	98 weeks	positive	
		150 ppm for 12 months	98 weeks	positive	
Inhalation	Sprague-Dawley Rats	75 ppm	lifetime	negative	Viola and Caputo, 1977
		200 ppm for 12 months		negative	
Inhalation	Rats (Wistar)	75 ppm 200 ppm for 12 months	lifetime	negative	Viola and Caputo, 1977
Inhalation	Rats (CD)	55 ppm	52 weeks	negative	Lee *et al.*, 1978

continued-

Table V-17 - Continued

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Rats	25 ppm 75 ppm for 18 months	104 weeks	negative	Rampy et al., 1977
Inhalation	Chinese Hamsters	25 ppm	74 weeks	negative	Maltoni, 1977; Maltoni et al., 1977
Oral (gavage)	Rats (BDIV)	50 mg/kg/day	120 weeks	negative	Ponomarkov and Tomatis, 1980
Oral (gavage)	Rats (Sprague-Dawley)	0.32 mg/kg·day 3.2 mg/kg·day 6.4 mg/kg·day 13 mg/kg·day	136 weeks	negative negative negative negative	Maltoni
Oral (drinking Water)	Rats (Sprague-Dawley)	7-9 mg/kg·day 10-14 mg/kg·day 20-30 mg/kg·day	104 weeks	negative negative negative	Rampy et al., 1977 Quast, et al, 1983
Oral (Gavage)	Rats (F344)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
	Mice (B6C3F1)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
Subcutaneous	Swiss mice			inactive as whole mouse initiator	Van Duuren, et al., 1979
		121 mg	single dose	active as initiator with phorbol myristate acetate	

VI. HEALTH EFFECTS IN HUMANS

A. Acute and Chronic Effects

CNS. At high concentrations, the DCEs possess anesthetic properties, as do other members of the chlorinated ethylene series. Although considerable research has been done on those compounds which were used as general anesthetics, little is known concerning the short-term or long-term effects of DCEs on the CNS. The CNS depressant effect has been described from unpublished data (Irish, 1963). A concentration of 4000 ppm was estimated as sufficient to produce rapidly a state resembling drunkenness and was judged likely to result in unconsciousness if exposure were continued. A single report has been made associating sensory disturbance in the facial areas controlled by the trigeminal nerve with an accidental exposure to 1,1-DCE (Broser et al., 1970). Subsequent evaluation, however, suggested that the toxic agent was either mono- or dichloroacetylene which was a contaminant of 1,1-DCE (Henschler et al., 1970). No further information is available on the CNS effects of these compounds.

Teratogenicity/Mutagenicity. No studies addressing mutagenic or reproductive hazards among 1,1-DCE-exposed populations have been reported (Bahlman et al., 1979).

Carcinogenicity. There are no published studies with adequate data to permit an evaluation of the carcinogenic risk of 1,1-dichloroethylene to humans (Bahlman et al., 1979). One study reported no excessive cancer risk among 138 workers occupationally exposed to 1,1-DCE, but methodological limitations of this study

(Ott et al., 1976) do not permit an adequate evaluation of the carcinogenic risk, since the number of individuals lost to follow-up in this study was high and the period of observation was relatively short. In a second study, mortality was examined among 629 workers occupationally exposed in a 1,1-dichloroethylene (1,1-DCE) production and polymerization plant where there was also exposure to vinyl chloride and acrylonitrile. It was reported that 7 of the 35 deaths that occurred were from malignant tumors. This was not greater than the expected number. Two bronchial carcinomas occurred in persons aged 35-39, whereas 0.08 were expected. However, no information was given on smoking habits (Theiss et al, 1977).

Immunological Response. A study was made of the effect of 1,1-DCE on the ability of murine and human lymphocytes to respond to mitogenic agents, allogenic lymphocytes or the antigenic nature of 1,1-DCE itself (Thurman et al., 1978). 1,1-DCE was found to cause no change in the response of lymphocytes to various stimuli and to have very low toxicity to lymphocytes.

Other Adverse Effects. Reports of effects on workers exposed to 1,1-dichloroethylene in combination with other vinyl compounds include liver function abnormalities, headache, vision problems, dizziness, weakness, fatigue and neurological sensory disturbances (NIOSH, 1979).

B. Epidemiology

There have been no adequate epidemiological studies of the dichloroethylenes that have not also involved exposure to other compounds e.g., vinyl chloride or acrylonitrile. The limited number of epidemiological investigations involving multiple compound exposures have been described above. These studies provide little evidence from which to define a human dose-response for the dichloroethylenes.

VII. MECHANISMS OF TOXICITY

The DCEs are readily absorbed and undergo rapid systemic distribution due to their lipid solubility and blood:gas partition coefficient. Therefore, there is fairly rapid equilibration throughout the body following exposure by any route of administration.

The DCEs, like other chlorinated hydrocarbons, have a depressant effect on the CNS which can lead to narcosis and, at high doses can ultimately cause death, probably due to respiratory depression. The exact neuronal mechanism of the CNS depression has not been determined.

Very little is known about the mechanism of toxicity of cis-and trans-1,2-DCE. However, there has been considerable work directed toward defining the mechanism of toxicity of 1,1-DCE. Aside from the CNS depressant effect mentioned above, which is probably due to 1,1-DCE itself, most of the acute and long-term toxic effects observed, e.g., hepatotoxicity, renal toxicity, mutagenicity and carcinogenicity, are due probably to the formation of toxic metabolites. It has been suggested that the acute toxicity of 1,1-DCE can be correlated to the amount of metabolite formed. For short-term inhalation exposures, mortality occurred in rats after the formation of 25-30 mg of metabolites/kg (Andersen et al., 1979b). Additionally, it has been shown that mice metabolize 1,1-DCE more rapidly than rats. There is a corresponding higher mortality resulting from a given dose with mice than with rats, presumably due to the formation of a greater amount of toxic metabolite (Short et al., 1977a; Maltoni, 1977; Jones and Hathway, 1978b).

The biotransformation of 1,1-DCE has been demonstrated to be a saturable process that follows Michaelis-Menten kinetics. At low doses, below the metabolic saturation point, the majority of an administered dose is biotransformed to water soluble products which are excreted via the kidney. However, when large doses of 1,1-DCE are administered by any route and metabolism is saturated, large amounts of untransformed 1,1-DCE are excreted via the lungs. Thus, although the single dose oral LD_{50} value for 1,1-DCE in rats is 1500-1800 mg/kg, a large percentage of the administered dose is exhaled without biotransformation. There is also a difference in the toxic effects caused by continual exposure to 1,1-DCE compared to those caused by repeated intermittent exposures. Whereas adverse reactions including increased lethality were observed in several species following continual exposures to 1,1-DCE concentrations as low as 5 ppm, no toxic effects were observed following exposure for 8 hr/day, 5 days/week for six weeks to 100 ppm (Prendergast *et al.*, 1967). With the intermittent exposure regimen, there was probably rapid elimination of untransformed 1,1-DCE between exposures, as well as opportunity for glutathione levels in organs to return to normal. Similarly, at high exposure concentrations, the acute inhalation toxicity was related to the duration of the exposure, i.e., the total amount of toxic metabolite formed when biotransformation was proceeding at V_{max}, rather than to the ambient concentration (Andersen *et al.*, 1979a). At low concentrations, it has been suggested that the rate of biotransformation of 1,1-DCE is limited by the blood flow to the liver. Since the rate at which an inhaled chemical is presented to the liver is related to pulmonary uptake, it would be expected that the smaller breathing volume (liters/kg/hr) in man relative to the rat would produce a corresponding slower rate of metabolism of 1,1-DCE in man (Andersen et al., 1980a) and the formation of smaller amounts of toxic metabolite(s).

The metabolism of 1,1-DCE is generally hypothesized to proceed via oxidation of the parent compound by microsomal enzymes of the mixed function oxidase system (MFOS), following one of several pathways: reaction with glutathione to produce a water soluble metabolite which undergoes renal excretion, presumably a detoxification mechanism reaction with macromolecules to produce covalently bound metabolites or rearrangement to form chloroacetyl chloride. This latter compound can either react with macromolecules or undergo hydrolysis to form chloroacetic acid, which reacts with glutathione to form a series of water soluble metabolites (see Figure IV-3). It is generally believed that reaction of these metabolites, i.e., 1,1-dichloroethylene oxide, chloroacetyl chloride and chloroacetic acid, with macromolecules leads to the observed toxic effects: hepatotoxicity, renal toxicity, mutagenicity and carcinogenicity.

The extent of hepatoxicity of 1,1-DCE appears to be related to the rate of formation of toxic metabolites relative to the rate of metabolism of these materials. Glutathione conjugation is apparently a crucial mechanism since increased susceptibility to liver damage has been demonstrated when hepatic glutathione concentration is decreased by any of several methods: fasting, pretreatment with certain chemicals, e.g., diethyl maleate, pretreatment with thyroxine or normal diurnal variation. Conversely, thyroidectomy, which increases hepatic glutathione concentration, decreases hepatotoxicity. It has been shown that there is an increase in 1,1-DCE metabolites covalently bound to liver macromolecules when the glutathione levels are decreased.

It has been demonstrated that a greater percentage of any administered dose of 1,1-DCE is transformed in mice than in rats. This has been attributed to greater activity of the cytochrome P-450 system in mice relative to rats which would lead to the formation of a larger amount of metabolite(s) in mice (Jones and Hathway, 1978b). This difference in biotransformation is reflected in a change in the ratio of the metabolites formed. Additionally, the administration of 1,1-DCE has a much more toxic effect on mice (oral LD_{50}:200 mg/kg) than on rats (oral LD_{50}:1500 mg/kg). One possible explanation for this difference is that 1,1-DCE and its metabolites are equally toxic to mice and rats, but the difference in the LD_{50} represents the relative ability of the two species to biotransform 1,1-DCE to the active metabolites. It has also been shown that there are much higher levels of covalently bound 1,1-DCE metabolites in both liver and kidney in mice than in rats.

The liver damage characteristically caused by exposure to other chlorinated hydrocarbons is injury to the endoplasmic reticulum. In contrast, 1,1-DCE causes nuclear changes, mitochondrial swelling and rupture of outer mitochondrial membranes. This indicates a basic difference in the mechanism of toxicity of 1,1-DCE. It has been suggested that chloroacetic acid may undergo further transformation to form a material, possibly monochlorocitric acid, that inhibits mitochondrial performance and is the molecular basis for hepatic injury (Jaeger, 1977).

Moore (1980) also has shown that the microsomal ATP-dependent calcium pump can be inactivated by 1,1-dichloroethylene metabolites.

1,1-Dichloroethylene was much more effective than chloroform and almost as effective as carbon tetrachloride when administered to male adult Sprague-Dawley rats ip (0.03-3 ml/kg body weight in corn oil). As a control, microsomal glucose-6-phosphatase activity was not inhibited. Since 1,1-dichloroethylene does not cause lipid peroxidation, such an effect was ruled out as being important. Further studies (Moore, 1982) showed that calcium pump activity could be inhibited by 45% within 20 minutes after a dose of 1.5 ml 1,1-dichloroethylene/kg in rats. The only other parameter which declined as rapidly was glutathione concentration. However, administration of diethylmaleate also produced glutathione depletion but did not cause calcium pump inhibition or release of microsomal calcium. The inactivation of the microsomal ATP-dependent calcium pump by 1,1-dichloroethylene metabolites also has been demonstrated _in vitro_ (Ray and Moore, 1982). These studies suggest that the microsomal calcium pump may be a critical target for 1,1-dichlorethylene alkylation and that disruption of cellular calcium homeostasis may be important in the toxicity of this chemical.

The renal damage caused by 1,1-DCE is characterized by vacuolization, tubular dilatation and necrosis. There is a considerable amount of covalent binding of 1,1-DCE metabolites in kidneys in both mice and rats. Mice have been shown to be more susceptible to kidney damage from 1,1-DCE than rats.

The mutagenic potential of the DCEs has been studied. Neither 1,1-DCE nor cis- or trans-1,2-DCE was mutagenic in bacterial systems without microsomal activation. However, in the presence of microsomal fractions from liver, kidney and lung from mice and rats, and from human liver, 1,1-DCE was shown to be mutagenic in *Salmonella typhimurium* and *E. coli* bacteria (Jones and Hathway, 1978c). Pretreatment of animals with modifiers of microsomal enzymes affected the bacteria mutagenicity of 1,1-DCE in the presence of microsomal preparations from these animals. These data have been interpreted by some investigators as showing that the mutagenicity of 1,1-DCE is due to the formation of an unsymmetrical, highly reactive metabolite which reacts with the DNA in the bacteria (Henschler *et al.*, 1976; Henschler, 1977; Henschler and Bonse, 1977). In contrast, biotransformation of cis- and trans-1,2-DCE produces symmetrical metabolies which are more stable and do not undergo reaction with DNA to produce mutations. The finding of increased mutation rates with 1,1-DCE in bacterial systems has not been confirmed in mammalian systems. Both mice and rats exposed to 1,1-DCE failed to produce dominant lethal mutations.

Several studies have been conducted to investigate the carcinogenic potential of 1,1-DCE. Using several routes of administration to Ha:ICR Swiss mice, it was shown that 1,1-DCE was inactive as a whole mouse skin carcinogen and inactive by subcutaneous injection, but was active as a skin tumor initiator in a two stage carcinogenesis assay using phorbol myristate acetate as a promoter (Van Duuren, *et al.*, 1979). In one carcinogenicity study, mice (Swiss, BALB/C, C56BL, and C_3H strains), rats (Sprague-Dawley) and hamsters were exposed to 1,1-DCE. At exposure to 10 ppm, there was no increased incidence of any tumor in any species. Exposure to 25 ppm of 1,1-DCE caused a statistically significant increase in kidney adenocarcinomas in Swiss mice, almost exclusively in the males (24/150 in males compared to 1/150 in females). Also, a statistically significant increase in mammary adenocarcinomas was found in Swiss mice at 25 ppm and in Sprague-Dawley rats at 100 and 150 ppm. No increase in kidney adenocarcinomas was found in Sprague-Dawley rats at exposures up to 200 ppm. Additionally, it has been reported that other studies by Maltoni found no statistically significant increased incidence of any tumor in BALB/C, C56BL or C_3H mice (Fishbein, 1979), or in hamsters (Maltoni, 1977; Maltoni et al., 1977). A second study using CD-1 mice and CD rats exposed to 55 ppm of 1,1-DCE found no statistically significant increase in incidence of kidney adenocarcinoma in mice or rats, while two rats developed hemangiosarcomas which were judged probably to be caused by 1,1-DCE (Lee et al., 1978). Three additional carcinogenicity studies conducted with rats (Sprague-Dawley, Wistar and BDIV strains) provided no unequivocal evidence for carcinogenicity of 1,1-DCE in rats (Viola and Caputo, 1977; Rampy et al., 1977; Ponomarkov and Tomatis, 1980). Further studies on the carcinogenic potential of 1,1-DCE in mice and rats sponsored by the National Toxicology Program have been completed which suggest that 1,1-DCE is not carcinogenic by gavage, at least at the doses used.

In summary, the carcinogenic potential of 1,1-DCE has been shown to be quite different from that of vinyl chloride. Vinyl chloride has been shown to produce hepatic angiosarcomas, sebaceous carcinomas, cutaneous skin tumors and forestomach papillomas in rats, mice and hamsters as well as mammary carcinomas in both rats and mice. Additionally, vinyl chloride has been found to cause liver angiosarcoma in humans. For 1,1-DCE, aspects of the reported carcinogenicity appear conflicting and indicate sex, species and strain specificity and differences due to the route of exposure. In mice, the most pronounced increases in tumor incidence caused by 1,1-DCE were kidney adenocarcinoma and mammary gland adenocarcinoma in Swiss mice. However, kidney adenocarcinomas were observed almost exclusively in male Swiss mice, and neither tumor type was observed in four other strains of mice. In rats, an increase in mammary gland adenocarcinomas was found in Sprague-Dawley rats in one study, but was not found in a second study using this strain or in studies using two other strains. Additionally, 1,1-DCE was found to be inactive as a carcinogen in hamsters.

It has been suggested that development of kidney adenocarcinomas in mice is due to the increased rate of biotransformation of 1,1-DCE in mice, which produces a higher level of reactive intermediates that can subsequently react with macromolecules, e.g., DNA (Maltoni, 1977; Hathway, 1977; Henschler and Bonse, 1977). A study has been made of the potential of 1,1-DCE to cause DNA alkylation, DNA repair and DNA replication in the liver and kidneys of mice and rats, and these results were compared with results obtained using the potent carcinogen dimethylnitrosamine (Reitz et al., 1980). Tumorigenic doses of dimethylnitrosamine produced relatively little tissue damage but caused a high degree of DNA alkylation and DNA repair synthesis. In contrast, tumorigenic doses of 1,1-DCE resulted in massive tissue damage but induced minimal DNA alkylation or DNA repair synthesis. These data were interpreted as suggesting that tumors observed in mice exposed to 1,1-DCE arise primarily through effects of the chemical on nongenetic components of cells.

Multiple Chemical Exposure: Potential for Interaction.

Jackson, et al.(1982) presented, in a poster session, the results of a study which investigated the interaction of 1,1-DCE with 1,2-dichloroethane (1,2-DCE). The compounds were administered via inhalation alone and together in several combinations. Their potential for acute hepatotoxicity and nephrotoxicity was assessed.

Male Sprague-Dawley rats were fasted overnight prior to exposure. Each was subjected in single 4-hour exposures to 200, 250 or 300 ppm 1,1-DCE alone, to 1400, 1600, 1800 or 2100 ppm 1,2-DCE alone or to combinations of 1,1-DCE and 1,2-DCE in the following ratios: 200/1200, 300/1800 or 400/2400 (see Table VII-1 for doses and animals/group). The dose combinations were chosen to reflect roughly equivalent potencies with respect to each compound's nephrotoxic effect.

Twenty hours after termination of exposure, the animals were sacrificed and blood collected. Serum sorbitol dehydrogenase (SDH) activity served as the indicator of hepatotoxicity. Nephrotoxicity was measured by kidney to body weight ratios, serum urea nitrogen and creatinine levels.

Changes in liver function as measured by serum SDH levels are shown in Table VII-1. As can be seen, 1,1-DCE, at all doses, caused very large increases in SDH levels, while changes after exposure to 1,2-DCE were less striking. The statistical significance of the effects, alone or in combination, were not reported. However, a cursory view of the data would suggest that effects seen after exposure to combinations of 1,1-DCE and 1,2-DCE were not significantly different from exposures to 1,1-DCE alone.

Table VII-1

Measure of Hepatotoxicity to Rats from Exposure to 1,1-DCE and 1,2-DCE

(Jackson, et al., 1982)

Treatment[a]	N[b]	serum SDH[c]
Control	10	1.8 ± 1.0
1,1-DCE		
200 ppm	4	94.0 ± 9.1
250 ppm	4	832.0 ± 158.1
300 ppm	4	706.7 ± 133.8
1,2-DCE		
1400 ppm	4	1.4 ± 1.4
1600 ppm	6	9.5 ± 1.7
1800 ppm	4	---
2100 ppm	6	17.0 ± 3.0
2400 ppm	6	33.2 ± 5.3
1,1-DCE/1,2-DCE		
200/1200	4	203.8 ± 110.1
300/1800	5	745.4 ± 116.2
400/2400	5	824.3 ± 151.4

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[a] Exposure concentration of 1,1-DCE and/or 1,2-DCE for 4 hours via inhalation

[b] number of animals, pooled controls

[c] serum sorbitol dehydrogenase ± S.E. measured at 30°C in mg/dl

An antagonistic effect on the kidney was demonstrated (see Table VII-2). When animals were exposed either to 300 ppm 1,1-DCE or 1800 1,2-DCE for four hours, significant increases occurred in the three parameters measuring nephrotoxicity. When animals were exposed to the same levels of each substance in combination, each parameter was decreased significantly from the levels noted for each chemical separately ($P<0.05$). A similar antagonism also was reported after exposure to a mixture of 200 ppm 1,1-DCE and 1200 ppm 1,2-DCE, although this mixture had no nephrotoxic effect (data not shown). With simultaneous exposure to 400 ppm 1,1-DCE and 2400 ppm 1,2-DCE, fewer rats died than would be expected based upon the LD_{50} of 1,1-DCE alone. The mean values for nephrotoxicity of this mixture was equal to 2400 ppm 1,1-DCE alone (data not presented).

The authors proposed that a possible mechanism for this antagonism could come from competition for metabolic pathways, since each compound shares common routes of metabolism in the liver, and, presumably, also, in the kidney. Thus, at these exposure levels, one or the other chemical could be inhibiting competitively the bioactivation or detoxication of the other. It would be important to establish whether or not this antagonistic interaction would occur at low levels of exposure, particularly in the range of occurrence in drinking water.

More recent studies have focused on the interaction of other chemicals with 1,1-dichloroethylene. As is the case with several halogenated alkanes, low doses of acetone can potentiate the toxicity of 1,1-dichloroethylene (Hewitt and Plaa, 1983). This study involved male Sprague-Dawley rats (150-300 g) and 50 mg/kg doses of 1,1-di-

TABLE VII-2

Antagonistic Effect of a Combined 1,1-DCE and 1,2-DCE Exposure on Nephrotoxicity

(Jackson, *et al.*, 1982)

Treatment[a]	N[b]	Kidney/body weight[c] (x ± S.E)	Serum SDH[d] (x ± S.E.)	Serum creatinine (x ± S.E)
Control	20	0.89 ± 0.07	8.25 ± 0.47	0.64 ± 0.01
300 ppm 1,1-DCE	4	1.66 ± 0.12	40.93 ± 11.30	1.79 ± 0.34
1800 ppm 1,2-DCE	4	1.57 ± 0.13	65.39 ± 4.87	4.51 ± 0.17
300 ppm 1,1-DCE + 1800 ppm 1,2-DCE	5	1.12 ± 0.10[f]	22.64 ± 7.45[f]	1.55 + 0.55[f]

[a] Four-hour inhalation exposures, controls pooled from several experiments

[b] number of animals in group

[c] g kidney/100g body weight

[d] mg urea nitrogen/10 ml serum

[e] mg creatinine/100 ml serum

[f] values significantly less than values for 300 ppm 1,1-DCE or 1800 ppm 1,2-DCE alone ($P < 0.05$)

chloroethylene (po in oil). After 24 hours, serum enzymes were from 2.5- to 10-times higher in animals treated with 5 or 10 mmol/kg acetone po plus 1,1-dichloroethylene in comparison to animals receiving 1,1-dichloroethylene only. Higher doses of acetone (15-30 mmol/kg) did not produce this effect, however. 1,1-Dichloroethylene administration can result in increased endogenous acetone production (Filser and Bolt, 1980); it is not known whether such endogenous production can have a potentiating effect on 1,1-dichloroethylene toxicity.

Both diethyl dithiocarbamate and carbon disulfide blocked the renal damage of 1,1-dichloroethylene in male ddY mice (Masuda and Nakayama, 1983). This protection is thought to be due to inhibition of enzymes which bioactivate 1,1-dichloroethylene. These authors also reported a hypothermic effect of 1,1-dichloroethylene (up to -10°C). Diethyl dithiocarbamate blocked the hypothermic response caused by administration of 1,1-dichloroethylene, but did not block the hypothermia which resulted from the administration of chloroacetyl chloride or chloroacetic acid, known metabolites of 1,1-dichloroethylene. This is consistent with the view that hypothermia caused by 1,1-dichloroethylene is mediated through metabolism.

Several efforts have been made to examine the influence of dietary factors on 1,1-dichloroethylene metabolism and toxicity. Nakajima, et al. (1982) varied protein, carbohydrate and fat components in diets fed to adult male Wistar rats and concluded that only low carbohydrate diets showed significant effects on the metabolism of 1,1-dichloroethylene. In this in vitro study, liver microsomes were examined for their ability to deplete 1,1-dichloroethylene from the atmosphere. Rats fed a low carbohydrate diet showed a two-fold increase in such a rate. In a subsequent study by the same group (Sato, _et al_., 1983), the effects of the low carbohydrate diet in this model were repeated (1.5-fold increase in the _in vitro_ rate of 1,1-dichloroethylene uptake). In addition, administration of a high level of ethanol to the rats for three weeks produced a 2- to 4-fold increase in the rate of 1,1-dichloroethylene uptake. On the other hand, studies by Siegers, _et al_., (1983) indicated that treatment of male Wistar rats with ethanol for seven days did not influence the _in vitro_ uptake of 1,1-dichloroethylene. However, such treatment increased the hepatotoxicity of a 125 mg/kg dose (po in olive oil) of 1,1-dichloroethylene (as judged by release of serum enzymes). Pretreatment of rats with ethanol for 24 hours prior to 1,1-dichloroethylene administration had no effect on hepatotoxicity, and simultaneous administration of ethanol decreased 1,1-dichloroethylene toxicity. Sieger, _et al_. (1983) also reported that dithiocarb and (+)catechin block the hepatotoxicity and acute toxicity of 1,1-dichloroethylene in rats.

VIII. QUANTIFICATION OF TOXICOLOGIC EFFECTS

The quantification of toxicologic effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Adjusted Acceptable Daily Intake (AADI) for the chemical is determined. For ingestion data, this approach is illustrated as follows:

$$\text{Adjusted ADI} = \frac{(\text{NOAEL or MEL in mg/kg})\ (70\ \text{kg})}{(\text{Uncertainty factor(s)})(2\ \text{liters/day})}$$

The 70 kg adult consuming 2 liters of water per day is used as the basis for the calculations. A "no-observed-adverse-effect-level" or a "minimal-effect-level" is determined from animal toxicity or human effects data. This level is divided by uncertainty factor(s) because, for these numbers which are derived from animal studies, there is no universally acceptable quantitative method to extrapolate from animals to the human, and the possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human toxicity data, an uncertainty factor is used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxins. The guidelines set forth by the National Academy of Sciences (Drinking Water and Health, Vol. 1, 1977) generally are used in establishing uncertainty factors. These guidelines are as follows: an uncertainty factor of 10 is used if there exist valid experimental results on ingestion by humans, an uncertainty factor of 100 is used if there exist valid results on long-term feeding studies on experimental animals, and an uncertainty factor of 1000 is used if only limited data are available.

In the quantification of carcinogenic effects, mathematical models are used to calculate the estimated excess cancer risks associated with the consumption of a chemical through the drinking water. EPA's Carcinogen Assessment Group has used the multistage model, which is linear at low doses and does not exhibit a threshold, to extrapolate from high dose animal studies to low doses of the chemical expected in the environment. This model estimates the upper bound (95% confidence limit) of the incremental excess cancer rate that would be projected at a specific exposure level for a 70 kg adult, consuming 2 liters of water per day, over a 70 year lifespan. Excess cancer risk rates also can be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. Current understanding of the biological mechanisms involved in cancer do not allow for choosing among the models. The estimates of incremental risks associated with exposure to low doses of potential carcinogens can differ by several orders of magnitude when these models are applied. The linear non-threshold multistage model often gives one of the highest risk estimates per dose and thus would usually be the one most consistent with a regulatory philosophy which would avoid underestimating potential risk.

The scientific data base which is used to support the estimating of risk rate levels as well as other scientific endeavors has an inherent uncertainty. In addition, in many areas, there exists only limited knowledge concerning the health effects of contaminants at levels found in drinking water. Thus, the dose-response data gathered at high levels of exposure are used for extrapolation to estimate responses at levels of exposure nearer to the range in which a standard might be set. In most cases, data exist only for animals; thus, uncertainty exists when the data are extrapolated to humans. When estimating risk rate levels, several other areas of uncertainty exist such as the effect of age, sex, species and target organ of the test animals used in the experiment, as well as the exposure mode and dosing rates. Additional uncertainty exists when there is exposure to more than one contaminant due to the lack of information about possible additive, synergistic or antagonistic interactions.

Non-carcinogenic Effects

The principal toxic effects of the dichloroethylenes following acute and longer-term exposures are upon the liver and kidney. In addition, like other members of the chlorinated ethylene series, they also possess general anesthetic and narcotic properties. Available data suggest that the CNS effects occur at exposure levels near or above those at which the liver and kidney effects are seen, even with acute exposures.

Acute toxicity, as measured by the LD_{50}, has been reported in several studies (Jenkins, et al., 1972; Andersen and Jenkins, 1977b; Freundt, et al., 1977; Andersen, et al., 1979a; 1977; Jones and Hathway, 1978b; NIOSH, 1978; Ponomarkov and Tomatis, 1980). These data are summarized in Table VIII-1.

Table VIII-1

Acute Toxic Effects of DCEs

Compound	Route	Species	Dose	Effect	Reference
1,1-DCE	oral	rat	200 mg/kg	LD_{50}	NIOSH (1978)
1,1-DCE	oral	rat	>1500 mg/kg	LD_{50}	Jenkins, et al. (1972)
		rat[a]	84 mg/kg	LD_{50}	Jenkins, et al. (1972)
1,1-DCE	oral	rat (395 g) (fasted)	>1500 mg/kg	LD_{50}	Andersen and Jenkins (1977b)
1,1-DCE	oral	rat (138 g) (fasted)	<50 mg/kg	LD_{50}	Andersen and Jenkins (1977b)
1,1-DCE	oral	rat (Male)	1800 mg/kg		Ponomarkov and Tomatis (1980)
		rat (Female)	1500 mg/kg		
1,1-DCE	oral	mouse (male)	217 mg/kg	LD_{50}	Jones and Hathway (1978b)
		mouse (female)	194 mg/kg		Jones and Hathway (1978b)
1,1-DCE	oral	dog	5750 mg/kg	LD_{50}	NIOSH (1978)
	iv	dog	225 mg/kg	LD_{50}	NIOSH (1978)
1,1-DCE	inhal	rat (fed)	15,000 ppm/4 hr	LC_{50}	Jaeger et al. (1974)
	inhal	rat (fasted)	600 ppm/4 hr	LC_{50}	Jaeger et al. (1974)
	inhal	rat (fasted)	200 ppm/4.1 hr 400 ppm/3.6 hr 500 ppm/13.0 hr 1000 ppm/2.4 hr 2000 ppm/1.4 hr	LC_{50}	Andersen et al. (1979a)
1,1-DCE	inhal	rat (fed)	6350 ppm/4 hr	LC_{50}	Siegel et al (1971)

Table VIII-1 (Continued)

Compound	Route	Species	Dose	Effect	Reference
1,2-DCE	oral	rat	770 mg/kg	LD_{50}	NIOSH (1978)
	ip	mouse	2000 mg/kg	LD_{50}	NIOSH (1978)
trans, 1-2-DCE	oral	rat (180-200 g)	1.0 ml/kg (1300 mg/kg)	LD_{50}	Freundt *et al.* (1977)
	ip	rat (180-200 g)	6.0 ml/kg (7800 mg/kg)	LD_{50}	Freundt *et al.* (1977)
	ip	mouse	3.2 ml/kg (4160 mg/kg)	LD_{50}	Freundt *et al.* (1977)

[a] Adrenalectomized

The wide range in lethality observed for 1,1-dichloroethylene is dependent upon a number of factors : 1) nutritional status-fasted animals are more sensitive than fed animals; 2) age and size-younger, smaller animals are more sensitive than older, larger ones; 3) species-exposure to the same inhalation dose results in more severe effects in mice than in rats; and 4) sex-with repeated dosing, male mice are more sensitive than females.

A number of studies on 1,1-DCE have been reported which are of sufficient length (subchronic or chronic exposure) to be considered potentially useful in the development of an acceptable daily intake (ADI) and adjusted acceptable daily intake (AADI). These studies describe good dose-response data which allow for the identification of no-observed-adverse-effect-levels (NOAELs) or minimal-effect-levels (MELs). In several of these studies, the animals were exposed to the substance orally, either by gavage or in their drinking water. Equivalent studies for cis- and trans-1,2-dichloroethylene are not available (the 1977 Freundt, et al. subchronic study with trans-1,2-DCE showed adverse effects at all tested doses). However, the information that is available suggests that although animals exposed to each of the three DCEs will have a greater amount of cis- and/or trans-1,2- isomer than 1,1-DCE present in their bodies at equilibrium, the non-carcinogenic toxicity induced by the 1,2- isomers appears to be somewhat less severe on an equivalent dose basis (Jenkins, et al., 1972; Filser and Bolt, 1979). Since the end-points of non-carcinogenic toxicity to all three DCEs are essentially identical, it is defensible to suggest that the ADI(s) developed for 1,1-DCE be applied to the 1,2-DCE isomers as well. It is understood that an added margin of safety would exist (perhaps 3-fold or so) based upon comparison of shorter-term exposure data. This decision would be consistent with a regulatory philosophy which seeks to avoid underestimating the potential risk. In addition, it would provide a basis for the development of ADIs and Recommended Maximum Contaminant Levels (RMCLs, or health goals) for the 1,2-DCE isomers. While, of course, it is preferred that ADIs and RMCLs be based upon data generated in studies of the specific compounds under consideration, the appropriate data for the 1,2- isomers do not exist at this time, while resolution of the problem of contamination of drinking water with these isomers of dichloroethylene is required in the short term. Therefore, it will be proposed that the ADI(s) and AADI developed for 1,1-dichloroethylene also be applied to each isomer of 1,2-dichloroethylene.

It has been reported that daily administration of 1,1-DCE to dogs for 97 successive days at dosages of 0, 6.25, 12.5 or 25 mg/kg bw caused no adverse effects (Norris, 1977; Quast, et al., 1983). The animals (4/sex/group) were given the compound as a 50% solution in peanut oil in a gelatin capsule. Each day, a control group of 4 animals/sex was given a capsule containing an amount of peanut oil equivalent to that given the dogs at the 25 mg/kg level.

No exposure-related changes were observed in appearance, demeanor, body weights or food consumption. The mean white cell counts of dogs receiving 6.25 or 25 mg/kg/day were significantly lower than control values on day 84 ($P<0.05$). However, these values were not significantly different from their own pre-exposure white cell counts. In addition, they were within the range of normal values observed in that laboratory. Therefore, the authors considered the differences to be unrelated to the ingestion of 1,1-DCE.

Female dogs receiving 6.25 mg/kg 1,1-DCE exhibited a significant decrease in BUN levels at day -7 and a significant increase in SGOT at day 85 ($P<0.05$). Males in that dose group showed elevated SGOT and SGPT at sacrifice ($P<0.005$). These comparisons were made with the concomitant controls. However, the investigators stated that the values were wihtin the range of normal values observed historically in that laboratory. No alterations in the clinical chemistry parameters were noted at the 12.5 or 25 mg/kg/day doses except for one high dose male that had an elevated SGPT on day 85 but not on day 97. No changes were seen in the SH content of the liver or kidneys.

No compound-related changes were reported in any of the parameters measured on urinalysis, in organ weight or organ: body weight ratios or on gross or microscopic examination of tissues. One male receiving 12.5 mg/kg/day had grossly enlarged kidneys, but no accompanying histopathology. The investigators determined that this finding was not comopund-related.

If one were to assume that the results of this study were appropriate for use in developing an ADI, it could be derived thusly:

$$\frac{25\ \text{mg/kg/day} \times 1.0 \times 70\ \text{kg}}{100 \times 10} = 1.75\ \text{mg/day}\ (\text{ or }\ 0.025\ \text{mg/kg/day for a 70 kg adult})$$

Where: 25 mg/kg/day = NOAEL (highest observed NOAEL; since no minimal or frank effect level was identified, the actual NOAEL may be higher in the dog)

1.0 = ratio of administered dose absorbed

70 kg = weight of protected individual

100 = uncertainty factor, appropriate for use wth NOAEL from animal studies with no comparable human data (longer-term exposure duration)

10 = uncertainty factor, appropriate for use of data from exposure duration significantly less than lifetime

Rsults were reported from a 90-day subchronic study in rats given nominal concentrations of 0, 50, 100 or 100 ppm of 1,1-DCE in their drinking water (Rampy, et al., 1977). The highest dose given was close to the limits of solubility for the compound (DeLassus and Schmidt, 1981). Ten rats/sex/group were used, with 2 rats killed on days 1,3,10 and 30 for determination of non-protein sulfhydryl groups in the liver and kidney. The mean daily dosage levels based upon the amount of water consumed were 0, 7.5, 12.6 or 25.6 mg/kg for the females and 0, 5.9, 10 or 19 mg/kg for the males.

Except for a decreased kidney:body weight ratio in males at the low dose, these were no statistically significant differences in organ weights or organ:body weight ratios at the termination of the study. The only histopathology noted was an increased cytoplasmic vacuolization of hepatocytes in livers of both sexes exposed to the highest dose. The investigators considered this to be a minimal change which would be reversible if the animals were removed from exposure to the chemical.

If one were to assume that the results of this study were appropriate for use in developing an ADI, it would be derived thusly:

$$\frac{10 \text{ mg/kg/day} \times 1.0 \times 70 \text{ kg}}{100 \times 10} = 0.70 \text{ mg/day (or } 0.01 \text{ mg/kg/day for a 70 kg adult)}$$

Where: 10 mg/kg/day = NOAEL (100 ppm or 10-12.6 mg/kg mean daily dose level)

1.0 = ratio of administered dose absorbed

70 kg = weight of protected individual

100 = uncertainty factor, appropriate for use with NOAEL from animal study, with no comparable human data (longer-term exposure duration)

10 = uncertainty factor, appropriate for use with data from exposure duration significantly less than lifetime

A two-year chronic toxicity/oncogenicity study was conducted in rats given nominal concentrations of 0, 50, 100 or 100 ppm of 1,1-DCE in their drinking water (Rampy, et al., 1977; Quast, et al., 1983). The time-weighted average mg/kg/day doses were 0, 7, 10 or 20 for the males and 0, 9, 14 or 20 for the females. Groups of 48 animals/sex/group were used, except for the controls (80/sex). Further details of the protocol and parameters measured are described in Chapter V.

No consistent treatment-related changes were observed in any parameter measured. The only pathological finding considered by the investigators to be treatment-related was in the liver of animals of both sexes in the high dose group. These microscopic changes, when present, usually were characterized by a minimal amount of mid-zonal hepatocellular fatty change. The degree of increase in this pathology was statistically significant in the males. A trend toward this increase was seen in males at the intermediate dose. No exposure-related changes were seen in males at the low dose. Minimal hepatocellular swelling and fatty changes were detected in females at all dose levels. No significant treatment-related hepatocellular necrosis was evident in either sex at any dose.

If one were to assume that the results of this study were appropriate for use in developing an ADI, it would be derived thusly:

$$\frac{10 \text{ mg/kg/day} \times 1.0 \times 70 \text{ kg}}{100 \times 10} = 0.70 \text{ mg/day (or } 0.01 \text{ mg/kg/day for a 70 kg adult)}$$

Where: 10 mg/kg = MEL (100 ppm or 10 mg/kg/day mean daily dose in males; trend toward increase in focal fatty changes in liver)

1.0 = ratio of administered dose absorbed

70 kg = weight of protected individual

100 = uncertainty factor, appropriate for use with animal data, with no comparable human data (longer-term exposure duration)

10 = uncertainty factor, appropriate for use in conversion of MEL to NOAEL

Ninety-day subchronic studies were performed to determine doses to be used in the chronic studies in the NTP carcinogenicity bioassay for 1,1-dichloroethylene (NTP, 1982). Groups of 10 rats and 10 mice of each sex were administered 1,1-DCE in corn oil by gavage 5 times/week at 0, 15,40, 100 or 250 mg/kg for 13 weeks. Vehicle control groups consisting of 10 males and 10 females of each species received corn oil alone. After 90 days, survivors were killed and necropsied. Unfortunately, no serum enzyme activities were determined in clinical chemistry studies. Monitoring of SGOT, SGPT, alkaline phosphatase and other indicators of liver function would have been useful in identifying a NOAEL.

Representative tissues from rats and mice receiving 250 mg/kg, from mice receiving 100 mg/kg and from control animals were examined microscopically. Livers from all other dose groups also were examined. Original examination of the lesions in the rat livers placed more emphasis on the changes seen in the animals at the lower doses whereas a review interpreted these changes to be less important.

Severe centrilobular necrosis of the liver was observed in the 3 females receiving 250 mg/kg that died before the end of the experiment. Minimal to moderate hepatocytomegaly was seen in the rest of the rats that received 250 mg/kg. Lesser degrees (minimal to mild) of hepatocytomegaly were seen in 6/10 male rats and 3/10 female rats that received 100 mg/kg. Various combinations of portal and hepatocellular atrophy were seen in all male rats (mild to severe in 9/10 and minimal in the other) and in 7/10 female rats (mild to moderate in 6/10 and minimal in the other) receiving 250 mg/kg. The rats receiving 100 mg/kg were affected to a much lesser degree, both in numbers and severity. Foci of cytoplasmic changes, primarily clear cell foci, were seen in 3/10 males and 3/10 females receiving 250 mg/kg. Fatty metamorphosis or cytoplasmic vacuolization or both, usually in minimal or mild degrees of severity, occurred in animals of most groups but had no distinct dose-response relationship. Nonetheless, the number of animals affected in each treatment group was significantly increased over control.

In the mice, centrolobular necrosis, hemorrhage and congestion of the liver were observed in males and females that died in the 250 mg/kg group. Cellular atypia of the liver (less severe than that seen in the rats) was observed in 7/10 males and 6/10 females receiving 100 mg/kg but not in animals receiving 250 mg/kg. At 40, 25 or 5 mg/kg, severity of hepatic lesions was dose-related. The incidence of hepatic lesions in males was dose-related and higher than in the females. The most frequently encountered change in mice exposed at 40 mg/kg or less was slight, sometimes moderate, fatty metamorphosis. Patchy foci of one or a few smaller cells with sparse cytoplasm were encountered much less frequently in mice than in rats.

Hepatic effects were considered to be minimal at 5 mg/kg.

If one were to assume that the results of this study were appropriate for use in developing an ADI, it would be derived thusly:

$$\frac{5 \text{ mg/kg} \times 1.0 \times 5 \times 70 \text{ kg}}{100 \times 10 \times 7} = 0.251 \text{ mg/day (or, } 0.0036 \text{ mg/kg/day for a 70 kg adult)}$$

Where: 5 mg/kg = MEL (based upon increased incidence of fatty livers in both sexes of rats)

1.0 = ratio of administered dose absorbed

70 kg = weight of protected individual

100 = uncertainty factor, appropriate for use use with animal data, with no comparable human data (longer-term exposure duration)

10 = uncertainty factor, appropriate for use in conversion of MEL to NOAEL

5/7 = conversion of 5 day/week dosing regimen to 7 day/week

In the chronic studies for the carcinogenicity bioassay, rats and mice were grouped 50/sex/group with controls receiving corn oil alone (NTP, 1982). Rats were dosed at 1 or 5 mg 1,1-DCE/kg, mice at 2 or 10 mg/kg. Doses were administered 5 times per week by gavage for 104 weeks.

Mean body weights of dosed and control rats of both sexes were comparable throughout the study. No compound-related signs of toxicity were observed. The number of accidental deaths may have influenced the incidence of late-appearing tumors in the control and low-dose males.

Several non-neoplastic lesions of possible significance were observed. The incidence of chronic inflammation of the kidney in both male and female rats was higher in the high dose groups than in the controls. Although the occurrence of chronic nephritis appears to be dose-related, this lesion is comon in aging rats.

Among the mice, the mean body weights of dosed male mice were lower than those in the control group (see Chapter V). Mean body weights of high dose and control females were comparable. Mean body weights of low dose mice of either sex were lower than those of high dose or vehicle control mice. No compound-related clinical signs were observed.

No significant differences in survival were observed between the groups of male mice. A significant reduction in the survival of female mice was observed in the low dose group when compared with the high dose group.

Non-neoplastic lesions including necrosis of the liver (focal, multifocal and diffuse) were observed more frequently in dosed mice than in controls (males=2%, 7% and 14%, respectively; females= 0%, 8% and 2%, respectively). The incidence of lung inflammation was slightly below that normally seen in 2-year old B6C3F1 mice.

If one were to assume that the results of this study were appropriate for use in developing an ADI, it would be derived thusly:

$$\frac{1\ \text{mg/kg} \times 1.0 \times 5 \times 70\ \text{kg}}{100 \times 7} = 0.5\ \text{mg/day (or, } 0.07\ \text{mg/kg/day for a 70 kg adult)}$$

Where: 1 mg/kg/day = NOAEL (lack of significant increase in incidence of chronic kidney inflammation in rats of both sexes

1.0 = ratio of administered dose absorbed

70 kg = weight of protected individual

100 = uncertainty factor, appropriate for use with NOAEL from animal data, with no comparable human data (longer-term exposure duration)

5/7 = conversion of 5 day/week dosing regimen to 7 day/week

Quantification of Non-carcinogenic Effects

Table VIII-2 summarizes the ADIs derived from the five oral studies which contain adequate dose-response data identifying NOAELs or MELs. It is apparent from the review of the available literature on 1,1-dichloroethylene that the liver is usually the most sensitive target and that the rat is more sensitive to the toxicity of 1,1-DCE than is the dog or mouse. Since suitable data from lifetime studies in rats are available, these should be the data of choice in deriving an AADI. The 2-year drinking water study by Dow (Rampy, et al., 1977; Quast, et al., 1983) and the NTP gavage bioassay in rats (NTP, 1982) both describe lifetime studies. Of the two studies, the 2-year drinking water study is the more appropriate since it exactly parallels the route of exposure best suited for developing drinking water guidance and standards.

If one were to assume that the drinking water study was the appropriate one for use in developing an AADI for the three isomers of dichloroethylene, the AADI would be derived thusly:

Step 1: $\text{AADI} = \frac{\text{ADI}}{2 \text{ liters}}$

Step 2: ADI = 0.7 mg/day

Step 3: $\frac{0.7 \text{ mg/day}}{2 \text{ liters}} = 0.35 \text{ mg/l/day}$

Table VIII-2

Possible ADIs for 1,1-Dichloroethylene

Experiment	Route of Exposure	Proposed ADI
90-day (dog)	gavage in oil	1.75 mg/day
90-day (rat)	drinking water	0.70 mg/day
2-year (rat)	drinking water	0.70 mg/day
90-day (rat)	gavage in oil	0.266 mg/day
2-year (rat)	gavage in oil	0.500 mg/day

The AADI reflects an allowable exposure for a 70 kg adult drinking 2 liters of water per day and whose sole source of exposure to the dichloroethylenes is via that drinking water.

It is further suggested that an AADI for total dichloroethylenes also be derived. This would address an instance in which more than one of the three isomers is present in a given analytical sample of finished drinking water. The AADI for total dichloroethylenes also should be 0.35 mg/l/day.

Carcinogenic Effects

1,1-Dichloroethylene. The carcinogenic potential of 1,1-DCE has been investigated in several species via various routes of exposure. The results of these studies are summarized in Table VIII-3. As can be seen, the results of most of the studies fail to support a significant, treatment-related increase in tumor incidence following exposure to 1,1-DCE. In no study in which the animals were exposed orally, either by gavage or in their drinking water, was there a significant tumor response. However, in some, but not all, of the inhalation studies, there were significant increases in tumor incidences. In addition, 1,1-DCE was active as an initiator by subcutaneous injection, when combined with phorbol myristate acetate as the promotor (Van Duuren, et al., 1979).

Assessment of the carcinogenic potential of 1,1-DCE is complicated further by the fact that the positive data developed by Maltoni, et al. are preliminary and have not been published or presented in a public forum for peer review.

Table VIII-3

Summary of Results from Carcinogenicity Studies with 1,1-DCE

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Swiss Mice	10 ppm 25 ppm for 12 months	98 weeks 98 weeks	negative positive	Maltoni, 1977; Maltoni et al., 1977
Inhalation	CD-1 Mice	55 ppm	52 weeks	negative	Lee et al., 1978
Not Reported	BALB/C Mice C56 BL Mice C_3H Mice	Not Reported Not Reported Not Reported	Not Reported Not Reported Not Reported	negative negative negative	Fishbein, 1979 Report of Maltoni studies
Inhalation	Sprague-Dawley Rats	10 ppm 25 ppm 50 ppm 100 ppm 150 ppm for 12 months	98 weeks 98 weeks 98 weeks 98 weeks 98 weeks	negative negative negative positive positive	Maltoni, 1977; Maltoni et al., 1977
Inhalation	Sprague-Dawley Rats	75 ppm 200 ppm for 12 months	lifetime	negative negative	Viola and Caputo, 1977
Inhalation	Rats (Wistar)	75 ppm 200 ppm for 12 months	lifetime	negative	Viola and Caputo, 1977
Inhalation	Rats (CD)	55 ppm	52 weeks	negative	Lee et al., 1978

continued-

Table VIII-3 - Continued

Route	Species	Dose	Study Duration	Carcinogenic Response	Reference
Inhalation	Rats	25 ppm 75 ppm for 18 months	104 weeks	negative	Rampy et al., 1977
Inhalation	Chinese Hamsters	25 ppm	74 weeks	negative	Maltoni, 1977; Maltoni et al., 1977
Oral (gavage)	Rats (BDIV)	50 mg/kg/day	120 weeks	negative	Ponomarkov and Tomatis, 1980
Oral (gavage)	Rats (Sprague-Dawley)	0.32 mg/kg·day	136 weeks	negative	Maltoni
		3.2 mg/kg·day		negative	
		6.4 mg/kg·day		negative	
		13 mg/kg·day		negative	
Oral (drinking Water)	Rats (Sprague-Dawley)	7-9 mg/kg·day	104 weeks	negative	Rampy et al., 1977 Quast, et al, 1983
		10-14 mg/kg·day		negative	
		20-30 mg/kg·day		negative	
Oral (Gavage)	Rats (F344)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
	Mice (B6C3F1)	1 mg/kg/day 5 mg/kg/day	104 weeks	negative	NTP, 1982
Subcutaneous	Swiss mice			inactive as whole mouse initiator	Van Duuren, et al., 1979
		121 mg	single dose	active as initiator with phorbol myristate acetate	

1,1-DCE has been tested in a number of short-term tests, some of which are considered to be useful in predicting mutagenic potential and also assisting in the evaluation of carcinogenic potential.

1,1-DCE was mutagenic to bacteria in the presence, but not the absence, of an exogenous metabolic activation system (Bartsch, et al., 1975; Griem, et al., 1975; Simmon, et al., 1977; Jones and Hathway, 1978c; Simmon and Tardiff, 1979). It also induced point mutations and mitotic gene conversions in Saccharomyces cerevisiae, but only after metabolic activation (Bronzetti, et al., 1981).

1,1-DCE was not mutagenic in the dominant lethal test in CD-1 mice exposed by inhalation to 40, 120 or 200 mg/m^3 1,1-DCE for 6 hours/day for 5 days (Anderson, et al., 1977). It also was not active in V79 Chinese hamster cells in the presence of 15,000 g liver supernatant from phenobarbital-treated rats and mice (Drevon and Kuroki, 1979), nor did it produce chromosomal aberrations in cytogenetic analyses of bone marrow cells following intraperitoneal injections (Cerna and Kypenova, 1977).

Reitz, et al. (1980) showed that 1,1-DCE alkylated DNA in the liver and kidney of both rats and mice, but only to a slight degree after 10 or 50 ppm 6-hour inhalation exposures. The highest degree of alkylation occurred in the kidney of mice exposed at the higher dose. In measuring DNA repair, the only statistically significant increase caused by 1,1-DCE was that occurring in the kidney of mice exposed at 50 ppm.

On the basis of the data available to date, IARC (1983) concluded that there is sufficient evidence to state that 1,1-DCE is mutagenic. Earlier, IARC (1979) had stated that the available experimental evidence indicates that the compound produces malignant tumors in mice and rats and that some of the tumors are similar to those produced by vinyl chloride. IARC said that this evidence is, however, limited by the fact that it is based partly on studies which were still in progress. A reevaluation will be made when IARC has the opportunity to review the data from completed studies by Maltoni, et al. as well as the Dow study and the NTP gavage bioassay. IARC's assessment of the available human data stated that these data were not adequate to permit assessment of 1,1-DCE's carcinogenic potential in the human (IARC, 1983).

EPA recently proposed guidelines for the assessment of mutagenic risk (U.S. EPA, 1984a). These guidelines are designed to address heritable (germ cell) mutagenic risk, not somatic cell risk. The Office of Drinking Water, in a preliminary application of the proposed guidelines, feels that there would exist limited evidence of human heritable risk following exposure to 1,1-dichloroethylene. The Office has asked the Reproductive Effects Assessment Group/Office of Health and Environmental Assessment to review and comment on ODW's assessment.

EPA also recently published proposed guidelines for carcinogen risk assessment (U.S. EPA, 1984b). These proposed guidelines identify a five-level weight of evidence classification scheme. Applying the proposed guidelines, the Office of Drinking Water determined, in a preliminary assessment, that the available data on the mutagenic and carcinogenic potential of 1,1-dichloroethylene directs the characterization of its carcinogenic potential into Group C: Possibly Carcinogenic to Humans.

Group C is proposed to include agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence: (a) definitive malignant tumor response in a single well-conducted experiment; (b) marginal tumor response in studies having inadequate design or reporting, (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) marginal responses in a tissue known to have a high and variable background rate.

1,2-Dichloroethylenes. Neither isomer of 1,2-dichloroethylene has been tested for carcinogenic potential in long-term studies. Therefore, it is not possible to make any judgment as to whether or not these compounds pose a human cancer risk.

Neither cis- nor trans-1,2-DCE was mutagenic when assayed with *E. coli* at similar concentrations used for 1,1-DCE (Griem, *et al.*, 1975). However, cis-1,2-DCE was found to be mutagenic in the host-mediated assay using *Salmonella* tester strains in mice, whereas trans-1,2-DCE was not found to be mutagenic under the same conditions (Cerna and Kypenova, 1977). These authors also reported that only the cis- isomer, of all three tested, produced chromosomal aberrations in bone marrow cells following intraperitoneal injections. Clearly, more studies must be done before conclusions can be drawn concerning the mutagenic and carcinogenic potentials of the 1,2- isomers of dichloroethylene.

Quantification of Carcinogenic Effects

1,1-Dichloroethylene. Using methodology described in detail elsewhere (U.S. EPA, 1980), the EPA Carcinogen Assessment Group calculated estimated incremental excess cancer risk associated with exposure to 1,1-dichloroethylene in ambient water, extrapolating from preliminary data obtained in the inhalation study in Swiss mice (Maltoni, *et al.*, 1977). CAG employed a linearized, non-threshold multistage model to estimate the upper bound 95% confidence limit of the excess cancer rate that would occur at a specific exposure level for a 70 kg adult ingesting two liters of water per day and 6.5 grams of fish a seafood ("fish factor") every day over a 70-year lifespan. The Office of Drinking Water Health Effects Branch modified these risks estimated for ambient water to reflect exposure to 1,1-dichloroethylene via drinking water alone (U.S. EPA, 1981). Recently, CAG recalculated estimated risks for drinking water exposure using updated data from the Maltoni inhalation study in Swiss mice (Maltoni, *et al.*, 1980; CAG, 1983).

A range of 1,1-dichloroethylene concentrations were computed that would be estimated to increase the risk by one excess cancer per million (10^6), per one hundred thousand (10^5) and per ten thousand (10^4) people over a 70-year lifetime. The ranges of concentrations developed by CAG and those modified by the Office of Drinking Water are summarized in Table VIII-4. As stated above, consumption of drinking water containing 24, 2.4 or 0.24 ug/l by a 70 kg adult over a 70-year lifespan at a rate of 2 liters per day is estimated to result in an excess cancer risk rate of 10^{-4}, 10^{-5} or 10^{-6}, respectively.

1,2-Dichloroethylenes. No data are available which indicate that these isomers have carcinogenic potential. Therefore, no estimation of risk can be made.

Table VIII-4

Drinking Water Concentrations and Estimated Excess Cancer Risk

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)		
	CAG[a] (1980)	ODW[b] (1981)	CAG[bc] (1983)
10^{-4}	3.3	3.4	24.
10^{-5}	0.33	0.34	2.4
10^{-6}	0.033	0.034	0.24
0	0	0	0

[a] Assumes daily consumption of 2 liters of water and 6.5 grams of fish/seafood by a 70 kg adult over a 70-year lifetime; number represents 95% upper bound confidence limit.

[b] Assumes daily consumption of 2 liters of water by a 70 kg adult over a 70-year lifetime; number represents 95% upper bound confidence limit.

[c] Considered to be the appropriate range of concentrations for estimation of risk following exposure via drinking water.

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